NOVEMBER, 1944 Vol. 120, No. 5

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ANNALS of SURGERY

A Monthly Review of Surgical Science and Practice

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ANNALS OF SURGERY

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EXPERIMENTAL STUDY OF THE HISTOPATHOLOGY OF BURNS: WITH PARTICULAR REFERENCE TO SITES OF FLUID LOSS IN BURNS OF DIFFERENT DEPTHS*

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IT IS AXIOMATIC that the key to understanding certain lesions of many organs is a knowledge of the special features of their blood supply. Yet, singularly little attention has been paid to the special features of the blood supply of human skin in discussions of the pathology of burns or in their classification. With the present-day emphasis on local fluid loss as a cause of burn shock, however, it becomes important to review the pathology of burns in relation to the blood supply of skin because it is from blood vessels that fluid is lost. Such a study is herewith reported.

MATERIAL AND METHODS

Selection of a Suitable Experimental Animal.—In preliminary experiments made on several common laboratory animals we tried to produce burns that resembled fairly superficial human burns. We were unable, however, to produce burns on the backs of these animals that demonstrated the erythema and blister formation that characterize this type of burn in man. This led us to reflect that the skin of man serves a different purpose from the skin of most very hairy and furry animals and, for this purpose, it has a very different blood supply. The skin of man serves as an organ for disseminating heat when the weather is hot and, hence, it is equipped with sweat glands and an extensive set of small blood vessels situated close to the epidermis. As our work progressed it became apparent that these superficial plexuses of vessels are responsible for the erythema and blister formation of superficial burns and that many common laboratory animals lack this extensive superficial blood supply because their skins are designed to serve primarily as insulation rather than as organs for disseminating heat. Hence,

* This research was assisted by a grant from the National Research Council of Canada.

Appreciation is due A. W. Carrie and E. C. Hunt who gave valuable assistance in performing the experiments.

these manifestations of superficial burns (erythema and blisters) cannot be produced in them. The histopathology of superficial burns in many laboratory animals, then, differs profoundly from that in man. We found, however, that the skin of the hog is similar to the skin of man in many respects. Wilson[1] points out that it is one of the few animals whose skin contains papillae. It sweats in hot weather and so, like man, uses its skin to disseminate heat. Its skin, therefore, contains a reasonably extensive plexus of small vessels in the papillary and subpapillary layers of the dermis and an abundant supply of sweat glands (Fig. 1). The hog, then, was selected as the experimental animal for these studies.

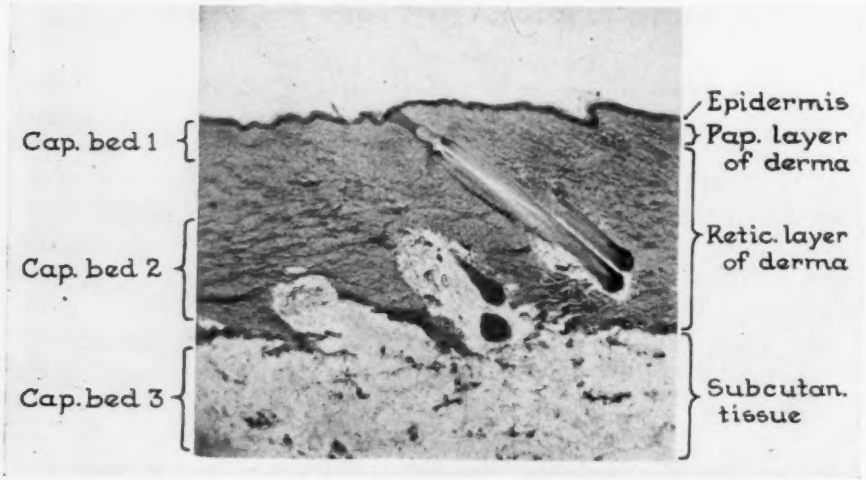


FIG. 1.—Low power photomicrograph of the skin of the back of a young hog. The location of the superficial plexuses normally concerned in the process of heat loss, and primarily concerned in superficial burns, is indicated as Cap. bed 1. The roots of the hair follicles and the secreting portions of the sweat glands are situated in pockets of areolar tissue in the lower portion of the derma. Three such pockets can be seen in this photograph. Cap. bed 2, which is primarily concerned in the more severe second degree burns, is confined to these pockets.

Methods for Producing Burns.—Young hogs, recently weaned, and weighing around 15 kilos. were used. They were anesthetized with ibatol, which was given either subcutaneously far removed from the burn site or intravenously. Burns were produced in two ways: By holding the base of a 25 cc. Erlenmeyer flask of boiling water against the shaved skin of a hog for different lengths of time, or by dipping a portion of the shaved back of a hog into a large bath of water heated to 80° C. for different lengths of time.

GROSS OBSERVATIONS

"Red" and "White" Burns.—There is a great deal of variation in the response of the skin in different areas in the hog. The skin of the back is thick. A flask held against it for four seconds and then removed produces a burn which quickly turns red. If held for seven seconds the red is of a deeper color. When the flask is held for from 10 to 20 seconds the color tends to be patchy, with both red and white areas present over the burned

surface. The white areas, moreover, tend to turn gradually red. But when the flask is held for from 25 to 30 seconds most of the burned skin is white and it tends to remain white. The skin of the abdomen requires much shorter exposures to produce the same effects.

In first degree burns produced by very short exposures large blisters do not form. But in the more severe superficial burns the epidermis tends to be raised slightly by underlying fluid and when it is lifted off its under surface can be seen to be wet.

In the more severe first degree burns and in second and third degree burns produced by this method the swelling is more noticeable. The swelling is greatest in the burns produced with the longer exposures and where the skin is thinnest.

In the larger burns produced by dipping the back of the hog into a water bath the gross appearances were similar to those observed after holding a flask against the skin. The time necessary to produce comparable burns, however, was different.

A Method for Determining the Depth of a Burn in the Hog.—It was observed that information could be gained about the depth of a burn in the hog by pulling on the hairs remaining in the burned areas. If the burn is superficial the hairs offer as much resistance to being pulled out as do hairs in normal skin but if the burn is deep the hairs offer little resistance to being pulled out. The reason for this will be given later.

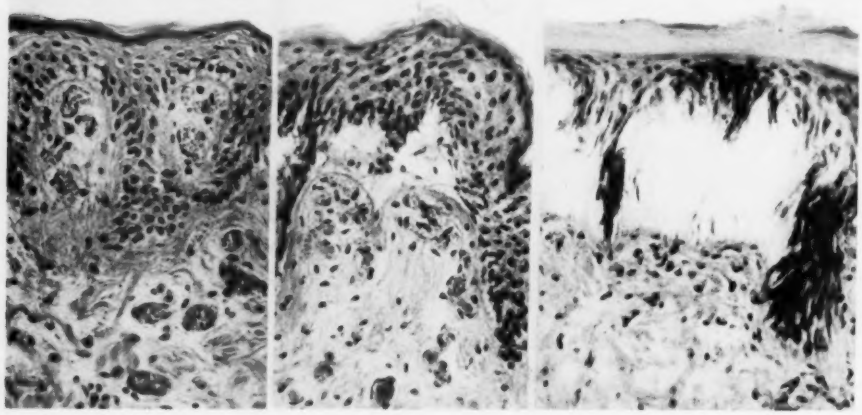
MICROSCOPIC OBSERVATIONS

Most of the substance of the skin of man and of most animals is relatively nonvascular. It consists chiefly of dense irregularly arranged connective tissue and the chief component of this is the intercellular substance collagen, a nonliving material. Hence, most of the skin does not need, nor is it supplied with, extensive networks of capillaries. There are, however, two important groups of capillary networks in the skin of man and the hog; (1) Several layers of networks situated in the papillary, and in the adjacent part of the reticular layers of the dermis together with loops extending up into papillae; these are concerned with allowing the skin to lose heat and they also nourish the epidermis above them; and (2) networks about the secreting portions of the sweat glands and the roots of hair follicles and also in the papillae of the latter. The sites of these capillary beds are indicated in Figure 1.

*First Degree Burns.**—In very mild first degree burns, produced by exposures of two or three seconds, the only change that can be observed in

*The three-degree classification is used in this paper: A first degree burn is considered to be one in which damage is confined mostly to the epidermis; a second degree burn one in which damage extends into the dermis without, however, destroying all of it or the more deeply situated portions of the hair follicles and sweat glands; and a third degree burn one in which the whole-thickness of the skin, including the more deeply situated epithelial elements, is destroyed.

histologic sections is a dilatation and congestion of the capillary loops of the papillae (Fig. 2, A). In slightly more severe first degree burns soon after the injury the capillaries of the papillae are dilated and congested and the lowermost cells of the epidermis above the papillae are hydropic. Later accumulations of fluid lift the epidermis from the derma as the hydropic cells give way (Fig. 2, B). A little later the epidermis becomes separated from the dermis by a still larger accumulation of fluid (Fig. 2, C). In fairly severe first degree burns there is also a marked congestion and dilatation of the blood vessels in the deeper part of the papillary layer and of the adjacent part of the reticular layer (Fig. 3).



A B C

FIG. 2.—Medium power photomicrographs of hog skin showing the development of a blister in a superficial burn. A. Specimen recovered 15 minutes after a five-second exposure to a flask of boiling water. It shows dilatation and congestion of the capillary loops of the papillae and the small blood vessels of the papillary layer. B. Specimen recovered one hour after a five-second exposure to a flask of boiling water. It shows the same dilatation and congestion of vessels as is seen in A but, in addition, it shows an accumulation of fluid in and under the deepest cells of the epidermis which is breaking away from the derma. This illustrates the beginning of a blister due to plasma leaking from the adjacent congested capillaries. C. Specimen recovered four hours after a six-second exposure to a flask of boiling water. In this the epidermis has become almost completely separated from the derma by fluid and is attached only at the sites of some of the interpapillary pegs.

To sum up: A histologic study of first degree burns shows that there is a dilatation and congestion of the superficial plexuses of capillaries and venules in the skin (the plexuses used for disseminating heat) and, in the more severe ones, that this is associated with an escape of fluid from these vessels. Part of this fluid may lift the epidermis from the dermis to form small blisters, and part causes an edema of the dermis. In our studies of burns in the hog we found that almost all blisters were situated between the epidermis and the dermis; and these findings make one question whether intra-epidermal blisters are as common in man as is generally believed, except in the skin of the palms of the hands and soles of the feet where the epidermis is thick.

Second Degree Burns.—In mild second degree burns many of the vessels in the superficial group of plexuses continue to function and leak fluid.

In severe second degree burns the whole superficial group of vessels is

mostly sealed off by the heat ("white" burns). For a while we were greatly puzzled as to how there could be so much fluid loss in this type of burn because the underlying dermis, as such, contains few capillaries. It was not until our histologic studies revealed an intense congestion and dilatation of the capillary beds associated with the deep secreting portions of the sweat glands and the deepests parts of the hair follicles (Fig. 4) that we found the answer. This congestion is associated with fluid loss, and the fluid that escapes from the capillaries associated with the deepest parts of the hair follicles loosens the attachment of the hairs. This explains why hairs can be pulled out so easily in this degree of burn—easily-pulled hairs signify

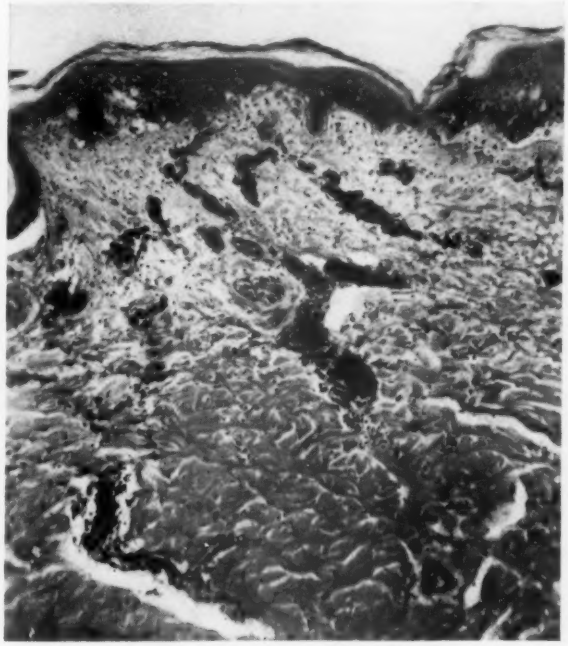


FIG. 3.—Low-power photomicrograph of a fairly severe superficial burn 48 hours after it had been produced. It shows, particularly, the dilatation and congestion of the blood vessels other than capillaries (which cannot be seen at this magnification) situated in the outer portion of the derma. The congested vessels appear black in the photograph.

fluid loss in the capillaries associated with the bottoms of the hair follicles, and, hence, a deep second-degree burn. In the hog, fluid lost from this capillary bed finds its way readily to the subcutaneous tissue.

Third Degree Burns.—In moderate second degree burns we did not observe evidences of great capillary congestion in the subcutaneous tissue and our findings suggest that much of the fluid that tends to accumulate in the subcutaneous tissue in this type of burn *has its origin in the skin*—it leaks down from the capillaries associated with the bottoms of hair follicles and secreting portions of sweat glands. But in very severe second degree burns and in

B

A

FIG. 4.—A. Medium power photomicrograph of a deep portion of a hair follicle four hours after a flask of boiling water had been held against the skin for 20 seconds. Close inspection shows that the capillaries associated with the hair follicle are tremendously congested; so much so that it suggests that a hemorrhage had occurred in the tissue.

B. High-power photomicrograph of the deep secreting portions of sweat glands from skin similarly treated. The capillaries about the sweat glands can be seen to be dilated and congested and the tissue containing them is distended with escaping fluid.

third degree burns fluid loss actually occurs from the capillaries of the subcutaneous tissue; we observed a marked congestion of the capillary beds in it and there were evidences of accumulations of fluid about them.

EXPERIMENTS WITH TRYPAN BLUE

The histologic studies reported above indicated that two groups of capillary beds in the skin could be involved in burns of different intensities, and that a third capillary bed, situated in the subcutaneous tissue, is involved in more severe burns. It was thought that it would be helpful to perform another type of experiment to help confirm, or deny, that these beds are the chief sites of fluid loss in burns of different intensities.

Trypan blue is a colloidal dye which can be injected intravenously into animals in a 1 per cent solution without noticeable harmful effects. It does not ordinarily escape from healthy capillaries fast enough to produce a very intense diffuse staining of the animal's tissues. Where plasma is escaping into tissue, however, the trypan blue seems to escape as well, and so such areas become of a deep blue color. We injected several young hogs with up to 110 cc. of 1 per cent solution per hog, either soon before or soon after burns were produced on them by the flask method. Thin slices of skin and subcutaneous tissue were removed from the burned areas at different time-periods, ranging up to three hours after the burns were produced, and examined with naked eye.

In general, the surface of first degree burns in an animal previously given trypan blue soon turns blue and slices taken from such burns, soon after the burn is produced, show a deep blue line along the superficial border of the dermis. Slices taken an hour or more later show the whole-thickness of the skin to be blue, but the most intense blue color is still at the upper border of the dermis. These experiments, then, also suggest that the most important source of fluid loss in a first degree burn is the superficial plexuses of small vessels in the papillary, and in the superficial part of the reticular layer of the dermis, and that, from here, fluid diffuses down throughout the whole-thickness of the skin.

In slices taken from fairly severe second degree burns made on the back of a hog, and in which the superficial vessels are destroyed by heat, the blue color is found to appear first, and in greatest intensity, along a wide line deep down in the dermis. From here the blue color spreads both up toward the papillary layer of the dermis and down into the subcutaneous tissue. These observations tend to confirm that the capillary beds associated with the deepest portions of hair follicles and the deep secreting portions of sweat glands are responsible for considerable fluid loss in this type of second degree burn.

If severe burns (20–30 seconds exposure) are produced on the abdomen of the hog, where the skin is much thinner than on the back, a deep blue color rapidly appears in the subcutaneous tissue.

The experiments with trypan blue tend to confirm the inferences drawn from the histologic studies, namely, that there are two capillary beds in the skin, and one in the subcutaneous tissue, which are the chief sites of fluid loss in burns of different intensities.

SUMMARY AND CONCLUSIONS

1. Burns in many common laboratory animals do not give information applicable to human burns because the skins of these animals are different from the skin of man in the important respect that they are not designed to serve as organs for disseminating heat in hot weather and so lack papillae and the extensive set of superficial plexuses of small vessels that characterizes the skin of man and which, in conjunction with sweat glands, allows the skin of man to disseminate heat in hot weather.

2. The skin of the hog is designed to allow that animal to disseminate heat in hot weather. It has papillae, abundant sweat glands and a reasonably extensive superficial blood supply.

3. In young hogs, first degree and mild second degree burns show erythema and, to some extent, blister formation. Microscopically, these phenomena are seen to be due to changes in the superficial plexuses of small vessels that normally function in allowing the animal to lose heat. These vessels become dilated and congested to cause the erythema, and they leak plasma to cause the swelling and the blisters. The absence of this superficial blood supply explains why erythema and blisters cannot be reproduced in many common laboratory animals in burn experiments.

4. In more severe second degree burns the skin surface tends to be white rather than red. Microscopically this is seen to be due to the superficial set of vessels being coagulated. Plasma loss in this type of burn originates from deeper capillaries. In this connection, it should be pointed out that the substance of the skin of both man and the hog is not evenly supplied with capillaries. We found that, in burns severe enough to seal off the superficial set, the next important set to become involved was that associated with the deepest portions of the hair follicles and the deep secreting portions of sweat glands. These become dilated and congested and leak plasma. The leaking plasma, moreover, escapes from the skin down into the subcutaneous tissue.

5. In more severe burns a third great capillary bed is affected, that of the subcutaneous tissue.

6. In the young hog information can be gained about the depth of a burn by pulling on the hairs in the burned area. If the burn is deep enough to involve the capillary beds associated with the deepest portions of hair follicles, there is edema of these. This loosens the attachment of the hairs so that they offer little resistance to being pulled free.

7. The dilatation and congestion of both the smaller and larger blood vessels associated with the various types of burns studied in these experiments, together with the small hemorrhages that were not infrequently

observed, serves to emphasize that extensive burns would tend to abstract significant quantities of whole blood from active circulation in addition to the plasma that is lost by leaking away from the smaller vessels.

REFERENCE

1 Wilson, J. A.: The Chemistry of Leather Manufacture. 2nd edit., 1929, The Chemical Catalog Co. New York, U. S. A.

EXPERIMENTAL STUDY OF THE TANNIC ACID TREATMENT OF BURNS: WITH PARTICULAR REFERENCE TO ITS EFFECT ON LOCAL FLUID LOSS AND HEALING*

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WHEN DAVIDSON[1] introduced the tannic acid method for treating burns he suggested that its efficacy was due to its precipitating proteins and so preventing absorption of toxins from the burn site. In the years that followed it became fairly generally accepted that the tannic acid treatment did indeed tend to diminish shock in burns. But the manner in which it accomplished this action became less certain as evidence accumulated to put increasing emphasis on fluid loss in and about the burn site as the cause of shock. It has, therefore, become of interest to determine whether tannic acid has an important function in tending to limit fluid loss in and about a burn and if so, how this is accomplished, and, furthermore, whether it acts in this manner with equal effectiveness in burns of all degrees or whether it could be expected to exert this action in only certain types of burns. The investigation herewith reported was undertaken to provide information on these points together with some others including the effects of tanning on healing.

MATERIAL AND METHODS

Young hogs were used as experimental animals for reasons given in the preceding paper.[2] They were anesthetized by either subcutaneous or intravenous injections of ibatol, and burns were produced on their shaved skins either by holding the base of a 25 cc. Erlenmeyer flask of boiler water against them for different numbers of seconds or by dipping their backs into the water at 80° C. for different lengths of time. The burns were tanned by applying a coat of 10 per cent tannic acid to their surfaces, and then after this had dried, a coat of 10 per cent silver nitrate, and then, finally, after this had dried, successive coats of tannic acid during the next few hours. A complete débridement was performed on many burns before tanning; in our hands this entailed scraping the surface with a sharp scalpel in order to remove completely the epidermis from the dermis. Tissue for paraffin sections was obtained from burns of different ages caused by different lengths of time of exposure, and treated in different ways.

* This investigation was aided by a grant from the National Research Council of Canada.

Appreciation is due Doctors R. P. McCaffrey, G. A. L. Ross and H. F. Whittaker for valuable assistance in carrying out the experiments.

OBSERVATIONS

The Reluctance of Tanning Agents to Penetrate Epithelium.—In our experiments the epidermis of the skin proved to be a barrier to the penetration of tanning agents; even dead epidermis prevented the tannic acid from reaching and combining with the collagen of the dermis. To obtain satisfactory tans we were forced to remove the epidermis before applying the tanning agents and this we did by scraping it off with a sharp scalpel. The ability of dead epidermis to prevent the penetration of tanning agents is illustrated in Figure 1.

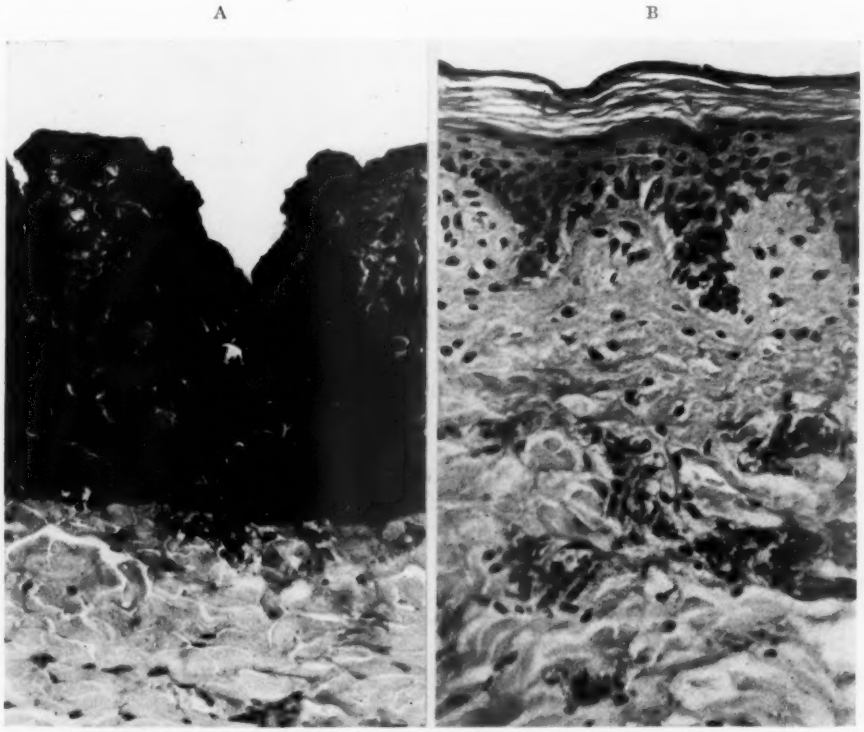

FIG. 1.—Low-power photomicrographs of two different areas in a second degree burn produced on a young hog. Both areas were treated with tannic acid for about an hour and a half. In A, however, the epidermis was removed before tanning was begun; in B it was left intact. These sections show how dead epidermis prevents tannic acid from penetrating into the dermis. A is well tanned and B exhibits no tanning.

Microscopic Features of Tanned Skin.—When tannic acid is applied in successive coats to a burned surface denuded of epidermis it penetrates remarkably evenly into the dermis, presumably by combining with the collagen in much the same fashion that it does in the manufacture of leather (Fig. 1A). The depth to which tannic acid penetrates to form tanned dermis depends upon how long the denuded surface is kept wet with tannic acid. About one hour's exposure caused a penetration of about one-sixth of the thickness of the dermis; many hours exposure resulted in a penetration of a quarter to a third of the thickness of the dermis (Fig. 2, A).

Frankly combining with the collagen of the superficial part of the dermis is, however, not the complete effect of tannic acid on the skin. It exerts a second effect, that of killing viable elements in the dermis for a considerable distance below the layer of dermis that is frankly tanned. The death of this second layer becomes apparent some hours after the tanning is finished and is evidenced by the gathering of leukocytes along a line some distance below the bottom of the frankly tanned layer. The line of leukocytes is well defined in 48 hours (Fig. 2, A).

FIG. 2.—Low-power photomicrographs of sections of tanned second degree burns.
A illustrates very heavy tanning caused by keeping the burned surface wet with tannic acid for about eight hours. Below the frankly tanned dermis a second layer of dermis, killed, but not tanned, by the tannic acid, can be seen. The lower border of this layer is marked by leukocytes. This tissue was obtained 48 hours after the burn was produced.
B illustrates a more lightly tanned burn. This section was obtained four days after the burn was produced, and it shows that new epidermis from hair follicles has grown along the line that is marked by leukocytes in A.

Tanning then, destroys a considerable thickness of dermis and the destroyed dermis consists of two parts, a more superficial layer that is frankly tanned and a deeper layer that is destroyed without being obviously tanned. Both these layers separate off in the eschar and the line of leukocytes seen in Figure 2 marks the line at which separation occurs. A tannic acid

eschar, then, contains two layers, an outer one that consists of frankly tanned dermis and a deeper one that consists of dermis killed, but not frankly tanned by the tannic acid (Fig. 4).

Why Tanning Could Be Expected to Diminish Fluid Loss in Certain Types of Burns.—In a previous paper[2] it was shown that there are three fairly distinct capillary beds from which fluid loss can occur in burns, and

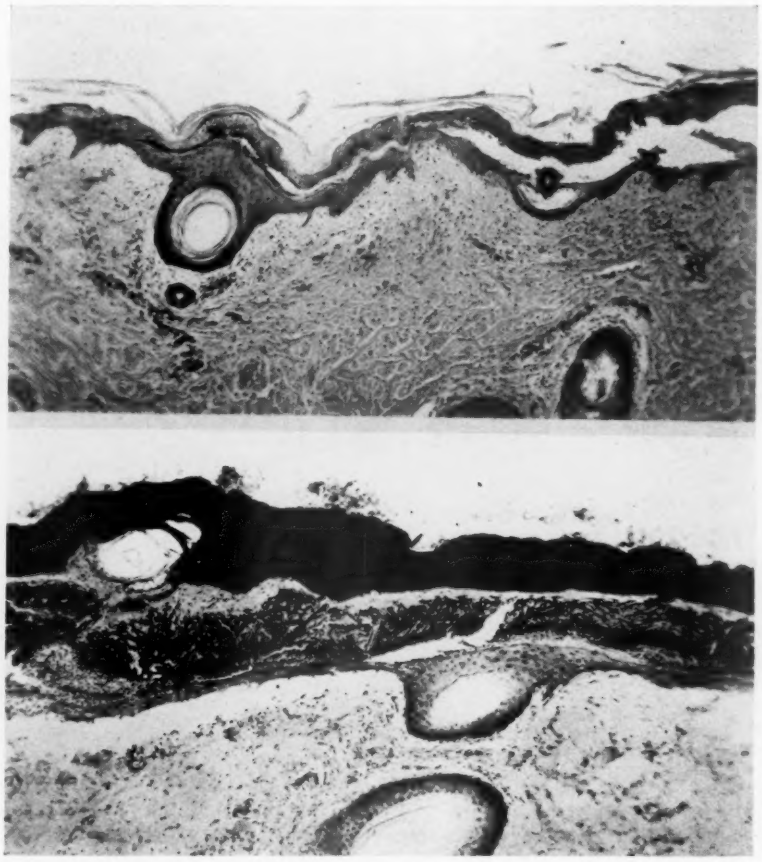

FIG. 3.—Very low power photomicrographs illustrating the healing of untanned and tanned burns produced by seven seconds exposure to a flask of boiling water. Both sections were obtained four days after the burns were produced.

The burn in the upper photograph was not débrided or tanned, and a new epidermis can be seen to have grown out from hair follicles underneath the old dead epidermis which it is displacing.

The burn in the lower photograph was débrided and tanned and a new epidermis can be seen growing out from hair follicles below the dermis that was killed by the tannic acid.

that each of these tends to be primarily involved in a certain type of burn. In first degree and in mild second degree burns it was shown that most fluid loss occurs from the superficial plexuses of vessels situated in the outer portion of the dermis. These vessels lie in the portion of the dermis that tends to be destroyed in effective tanning of the skin, hence, it could be

expected that tanning, by destroying the portion of the dermis that contains the leaking vessels, would tend to prevent fluid loss in this sort of burn.

In deeper burns, however, it has been shown[2] that fluid loss occurs chiefly from the capillaries associated with the deeper portions of the sweat glands and hair follicles, of even from the capillaries in the subcutaneous tissue. These capillary beds are too deeply situated to be incorporated into the layer of dermis that is reached and destroyed by the tannic acid, hence, tanning could not be expected to diminish fluid loss from these deeper burns in the same direct way that it does so in first and mild second degree burns.

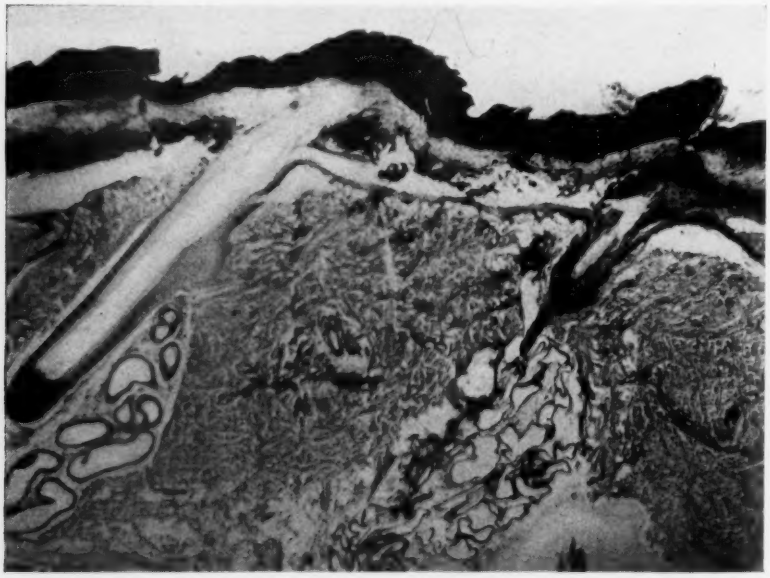

FIG. 4.—Very low power photomicrograph to show the state of healing in a tanned burn produced by seven seconds exposure to a flask of boiling water at four days. This illustrates very clearly how the epithelium grows out from the deeper portions of hair follicles to spread along under the eschar. Such separation of the eschar as has occurred is probably due to artefact.

Experiments with Trypan Blue.—In these an attempt was made to compare the amount of plasma loss in tanned burns with that in untanned burns by performing experiments in animals given trypan blue intravenously and then estimating the amount of dye that leaked out in the treated and untreated sites. To do this two sets of comparable burns of all degrees were made by the flask method on a young hog and tanning was begun on one set immediately. One-half hour after the burns were produced the intravenous injection of a 1 per cent solution of trypan blue was begun and this was continued at a slow rate for from one to three hours and quantities up to 200 cc. were given, although 100 cc. was the usual amount given a 15-kilo hog. At the termination of the experiment slices were cut from the various burn sites and the amount and position of deep blue color on the cut surface was observed.

The results in first and mild second degree burns were not consistent, but in many instances the difference between the amount of trypan blue that leaked out in the skin in a tanned burn and an untanned one was impressive, there being far more trypan blue leakage in the untanned burns. It was observed, furthermore, that keeping the tanned skin dry assisted greatly in limiting the escape of trypan blue from the burn site, indeed, drying *denuded* dermis, even without tanning it, was very efficacious in preventing trypan blue leakage from a denuded first or mild second degree burn.

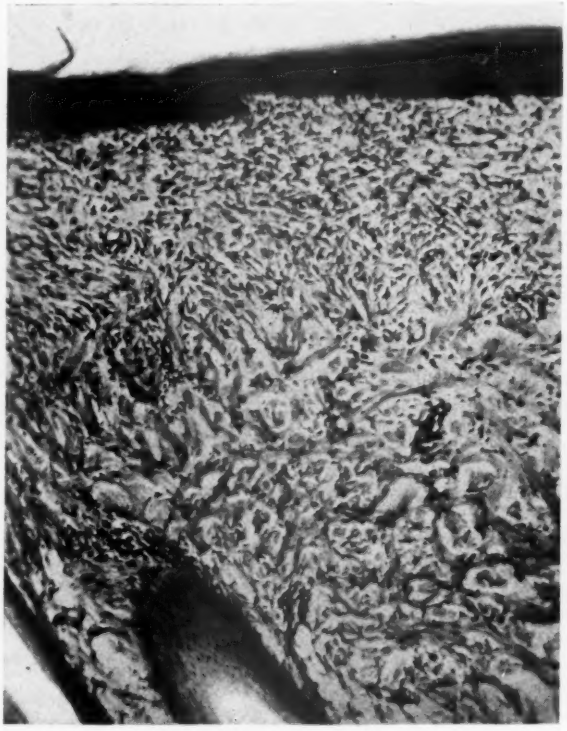

FIG. 5.—Low-power photomicrograph of a heavily tanned mild second degree burn 11 days after it was produced. This illustrates how heavy tanning necessitates the restoration of almost half the dermis and this occurs through the medium of granulation tissue wich can be seen in this section to occupy almost the upper half of the dermis. Epithelization is complete.

In deeper burns, where the fluid loss occurs from deeply situated capillary beds, tanning was found to exert little or no effect on the amount of trypan blue that escaped at the burn site.

Effects of Tanning on Healing.—In effective tanning, the superficial layer of the dermis is destroyed by the penetration of tannic acid. In the healing of a tanned burn a new skin surface forms along a line parallel to, and a short distance below, the bottom of the layer of dermis that is frankly tanned (Figs. 3 and 4). In the healing of a tanned burn there must be,

therefore, (1) the formation of a new epidermis, and this develops from the epithelium of hair follicles (Figs. 3 and 4); and (2) a restoration of the superficial layer of the dermis, and this forms through the medium of granulation tissue (Fig. 5).

It is obvious, then, that tanning must necessarily slow the healing of a very superficial burn in which the complete thickness of the epidermis and the superficial layer of the dermis is not destroyed by the heat. But in our experiments this consideration proved to be more theoretical than practical. In burns produced by 4, 7, 10, 15, 20 and 30 seconds exposure to a flask of boiling water and allowed to heal for four days we found little difference in the state of epithelization in the untanned and tanned burns (Fig. 3). This is because in all these burns (with the exception of a few areas in the four second burns) it was apparent at four days that the original epidermis had been destroyed by the heat and that healing demanded the regeneration of a new epidermis from hair follicles, and this, in our experience, formed as readily under a tan as it did under an eschar of dead untanned tissue. In the burns produced by 4 and 7 seconds exposure, epithelization from hair follicles was almost complete in four days time in both the tanned and untanned burns. In the 10-, 15- and 20-second burns there was considerable cellular activity in the hair follicles and some prongs of epithelium were seen extending out along the line of separation between dead and living tissue. In the 30-second burns all the epithelium in most of the hair follicles was dead and there was new growth in only a few of them.

In untanned mild to moderate second degree burns we observed that persistence of dead epidermis over the burn made considerable difference in the nature of the healing process. If the epidermis was detached and the dermis exposed to air, the superficial layer of the dermis dried and subsequently separated off in much the same manner as a tannic acid eschar with epithelium having formed below it. When the dead epidermis remained adherent to the dermis, however, it acted in a protective fashion and if the burn was not too severe it tended to preserve the superficial portion of the dermis so that epithelium from hair follicles could grow along under the old epidermis to take up its position on the original dermis.

To sum up: Our experiments gave little indication that tanning slows the process of epithelization except in very superficial burns. In the less severe second degree burns, however, tanning kills more dermis than would otherwise die (unless it is exposed and becomes dry), therefore, tanning demands a more extensive regeneration of dermis than would otherwise be necessary in this sort of burn.

SUMMARY AND CONCLUSIONS

1. In the young hog, either living or dead epidermis prevents the absorption of tannic acid into the dermis of the skin.

2. When dead epidermis is thoroughly removed from the surface of a burn, tannic acid penetrates in a remarkably even fashion into the dermis.

3. In our experiments, the depth to which tannic acid penetrated depended on how long it was applied, and tans that ranged from about one-sixth to almost one-half the thickness of the dermis were obtained by different lengths of treatment.

4. The application of tannic acid not only destroys the superficial layer of dermis with which it combines to form tanned skin; it also destroys a layer of dermis below that which is frankly tanned. The deep border of this second layer is usually soon marked by a line of leukocytes and it is along this line that reepithelization occurs in healing.

5. The superficial layer of dermis destroyed in efficient tanning contains most of the capillaries and venules of the superficial plexuses of vessels that in both man and the hog are normally concerned in temperature regulations and from which most of the fluid loss occurs in first and in the milder forms of second degree burns. By directly destroying the dermis containing these vessels it could be expected that tanning would tend to diminish fluid loss from this sort of burn.

6. Some experiments with trypan blue indicated that tanning diminished leakage in this type of burn, but other experiments were not convincing. When denuded tanned dermis was allowed to dry, however, experiments with trypan blue showed very convincingly that plasma leakage in this type of burn was greatly diminished by the combined procedure.

7. Experiments with trypan blue gave no indication that tanning materially affects plasma loss in deeper burns in which the superficial plexuses are mostly sealed-off by the heat and leakage is primarily from the capillaries associated with the bulbs of the hair follicles and the deep secreting portions of the sweat glands or the capillaries of the subcutaneous tissue, all of which are deep to the dermis destroyed by the tannic acid.

8. In very superficial burns where the epidermis is not completely destroyed the tannic acid treatment slows healing slightly because effective tanning always demands the formation of a new epidermis from hair follicles and a regeneration of the layer of dermis destroyed by the tannic acid. But in any but the most superficial burns the whole epidermis is destroyed by the heat and a new epidermis must form in any event, and this forms as readily under a tan as not. Hence, in any but very superficial burns tanning does not materially slow epithelization although it frequently demands the restoration of more dermis than might otherwise be necessary.

9. If these experiments have any clinical application it is, perhaps, that if the tannic acid method of treating burns has a use it is in the sort of burn in which most of the fluid loss occurs from the superficial plexuses of vessels that are normally concerned in temperature regulation, and that to be effective in preventing fluid loss from these the tan should be kept dry. The work provides no evidence to suggest that the tannic acid treatment would be equally efficacious in the more severe second degree burns or in third degree

burns where plasma loss occurs primarily from capillary beds out of reach of the tan.

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REFRIGERATION IN CLINICAL SURGERY*

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DURING RECENT YEARS refrigeration has been employed increasingly in the surgical treatment of gangrenous limbs. Its value remains in dispute chiefly because of a lack of satisfactory information regarding the effect of cooling on the healing of the wounds and on the progress of infection.

Enough general knowledge pertaining to the effect of cold has accumulated to warrant its analysis to determine, if possible, the advantages and disadvantages which might be expected to follow from prolonged cooling of tissues. Such knowledge should serve as a basis for the evaluation of measures involving the use of refrigeration in clinical surgery. Because the tourniquet has usually been employed in conjunction with refrigeration in the treatment of patients, any discussion of the merits and harmful effects of refrigeration preferably should include a consideration of the effects of the tourniquet. In this paper a discussion of the effects of cooling and of the effects of asphyxia produced by the application of a tourniquet will be followed by the presentation of cases in which a form of treatment in harmony with the implications of established physiologic principles has been employed.

THE EFFECT OF REFRIGERATION ON TISSUES

Within physiologic limits the velocity of most biologic processes varies directly with the temperature. At temperatures close to freezing there is almost complete cessation of cellular activity. Another pertinent observation is that conduction in a nerve trunk fails at or below certain critical temperature levels (25° to 30° C. in warm blooded animals),[1] thus accounting for the phenomenon of refrigeration anesthesia.

The changes which occur during and following the prolonged cooling of an extremity are of particular interest. While the tissues are cooled they are anesthetic and their metabolism is greatly diminished. After exposure to cold (3° to 4° C. for 24 to 96 hours) rats' tails show marked degeneration of nerves and muscles in the cooled areas.[2] The dog's forelimb, after immersion in cold water, exhibits edema and paralysis of the involved member, and these signs are followed by degeneration of the cooled peripheral nerves.[3] Similar, but more marked, changes are seen sometimes in shipwrecked sailors on exposure to cold and wet for varying periods. Such individuals may develop long-standing vascular and neurotrophic disturbances, and, in the most severe cases, gangrene of the feet.[4] Thus, the magnitude of tissue changes resulting from exposure to cold may be considerable. Although

* The experimental basis for this report was made possible by a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Washington University School of Medicine, St. Louis, Mo.

low temperatures may produce some injury by a direct effect upon living cells, there is rather general agreement that cold causes ischemia of the cooled part, and that lack of oxygen is responsible for most of the damage. During cooling there is an accumulation of tissue metabolites, which, after the cooling agent is removed, causes reactive hyperemia and other changes similar to those following the removal of a tourniquet (*q.v.*) although as a rule the changes are not profound enough to produce systemic effects.

Since normal tissues are damaged by cooling, the cells in areas undergoing reparative and inflammatory changes also would be expected to be affected adversely. Inhibition of healing of wounds during refrigeration has been shown to occur in the experimental animal by Large and Heinbecker.[5] Their studies also demonstrated that following the cooling period wound healing was delayed, the degree of delay being roughly proportional to the duration of the cooling period. Degenerative changes were shown to occur in the nerves of cooled extremities,[3] and these are considered responsible, in part at least, for the delay in the healing of wounds long after the actual exposure of the tissues to cold has ended.

Brooks and Duncan,[6] in carefully controlled experiments, observed that the inflammatory reaction to intradermal injections of bacteria and of oil of turpentine was inhibited during the cooling period. Following refrigeration the inflammatory reaction in injected areas was slightly greater than in the controls, with possibly some increase in actual necrosis. Bruneau and Heinbecker[7] found that during the cooling period no inflammatory response developed to *Streptococcus hemolyticus* injected subcutaneously and into joints of dogs' limbs, while after refrigeration the tissues exhibited a decrease in growth restricting action toward the bacterial organisms, the inflammatory reaction being more marked than in the controls. Large and Heinbecker[5] studied the healing of wounds treated by delayed suture after 24- or 48-hour cooling periods, and found that the refrigerated wounds showed a much higher incidence of gross infection, with suppuration, than did the uncooled controls.

THE EFFECT OF A TOURNIQUET

The tissues distal to the area of constriction are ischemic, and if rendered so for a sufficient time, undergo degeneration. Lewis[8] has shown that muscle fibers fail to recover their ability to contract when deprived of their blood supply for 6 to 8 hours; nerves die after 12 to 20 hours, the skin after 24 to 48 hours of ischemia. The tourniquet itself, if narrow and tight, may, by direct pressure on nerves, cause temporary paralysis. During the period of constriction, metabolites causing vasodilation accumulate, so that after the tourniquet is released, a period of reactive hyperemia ensues. If the mass of tissue distal to the tourniquet is large, release of the constriction may result in shock and even in death.

The effect of a tourniquet on the progress of infection varies with the duration of the period of ischemia. The cessation of blood flow presages

an interruption of the inflammatory reaction, which is inimical to the controlling of the infection following removal of the tourniquet. However, if a tourniquet be applied tightly enough to a limb proximal to a gangrenous or infected area, the obliteration of vascular and lymphatic channels at the level of constriction will prevent absorption of toxins and bacteria from the involved region into the general circulation. This beneficial effect will continue as long as the tourniquet is in place, unless the disease process is able to spread above the level of constriction by direct continuity of tissue.

EFFECT OF A TOURNIQUET AND REFRIGERATION USED SIMULTANEOUSLY

The survival time of a tightly constricted limb is prolonged greatly by refrigeration of the part. This was shown experimentally by Allen,[9] and demonstrated, conclusively, to be true by Brooks and Duncan,[10] who found that rats' tails rendered completely ischemic in a pressure apparatus lived many hours longer without the subsequent development of gangrene when exposed to temperatures of 1° to 15° C. than did those at room temperatures. The other effects of these agents used together can be predicted from the known changes following their individual or separate applications.

In summary, then:

a. The benefits of refrigerating an extremity include loss of sensation and diminution of absorption of noxious agents from the cooled area, while the disadvantages lie in a subsequent delay in wound healing, a greater risk of infection, and a varying degree of actual damage to refrigerated tissues left *in situ*.

b. The benefits of the application of a tourniquet to a limb refrigerated *above* the proposed level of amputation include anesthesia and the elimination of absorption of noxious agents, with increased duration of viability of the completely ischemic tissues, while the ill effects, again, include delayed wound healing, greater risk of infection, and actual tissue damage to the refrigerated stump.

c. The benefits of refrigeration with the application of a tourniquet *below* the proposed level of amputation of a limb, as in the other instances, include loss of sensation and elimination of absorption of noxious agents from the part; the further advantage of eliminating interference with wound healing and the spread of infection also is assured.

CLINICAL APPLICATIONS

The management of critically ill patients with gangrenous extremities frequently involves the control of toxemia, of infection, of anemia and of derangements in metabolism. If absorption of toxins from the involved limb can be prevented for a time, the patient's general condition can be improved enough so that operation may be performed with much less risk. This can be accomplished most simply by a tourniquet about the limb above the involved area, but below the level of proposed amputation. Such a plan was

followed not infrequently during the last war, and, more recently, Maxeiner (1941)[11] reported the successful use of "temporary tourniquet amputation" in 12 cases. Adolph[12] advocated a similar method. The results obtained, in general, were satisfactory, but the patients had severe pain until the tourniquet produced anesthesia, and occasionally infection developed above the level of constriction.

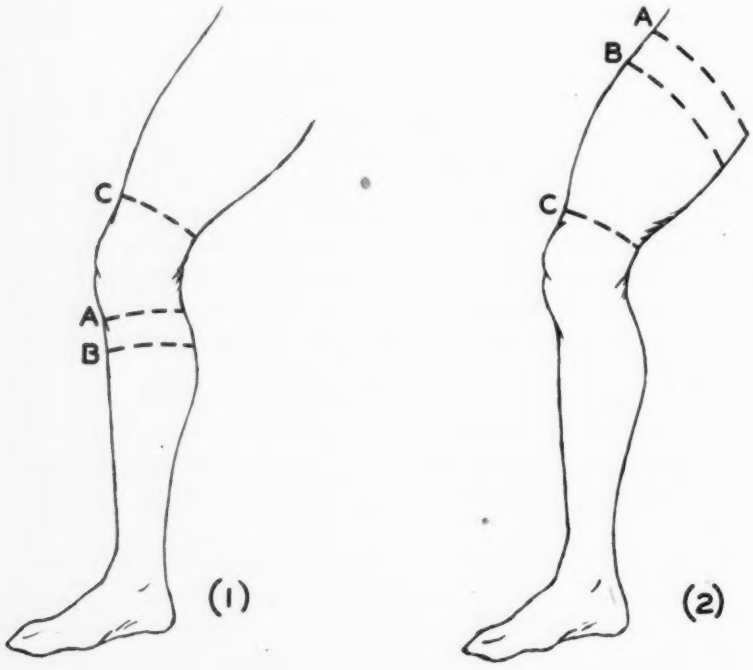

FIG. 1.—Diagrams of methods of use of refrigeration and the tourniquet before operation. A. Level of refrigeration. B. Site of application of tourniquet. C. Level of amputation.

(1) Diagram showing the advocated level of refrigeration, A and the site of amputation. C. Note that the distance AC is considerable.

(2) Diagram showing the method of refrigeration anesthesia as employed by Allen, and others. Note that the large mass of refrigerated tissue AC is not excised.

Allen, in certain experiments,[13] found that a tourniquet could be applied painlessly, if the limb were refrigerated first. He suggested the use of refrigeration together with a tourniquet in the preparation of poor-risk patients with gangrenous feet for amputation, and introduced the clinical use of refrigeration anesthesia for such operations.[14] The type of procedure advocated by him, and his coworkers,[15] is indicated in Figure 1. The disadvantage of this method appears to lie in the fact that much of the cooled, and, therefore, damaged tissue is not excised. It is felt preferable that all refrigerated tissue should be removed at operation. This can be done by applying the tourniquet and the cold distal to the level of amputation as indicated in Figure 1.

ILLUSTRATIVE CASES

Case 1.—H. H., a 54-year-old white female, known to have diabetes mellitus, was admitted to the Barnes Hospital, April 10, 1943, with a three-month history of spreading infection of the right foot. Examination showed a toxic, drowsy, but rational female, who seemed critically ill. The temperature was 39.6° C. The right 5th toe was absent, and there was a large, foul, necrotic, sloughing ulcer on the lateral aspect of this foot, from which thick pus could be expressed. Induration and swelling were present up to the ankle. There were no palpable arterial pulsations in either foot, but both popliteal pulses could be felt. Laboratory findings included Hb, 42 per cent; W. B. C. 17,000;

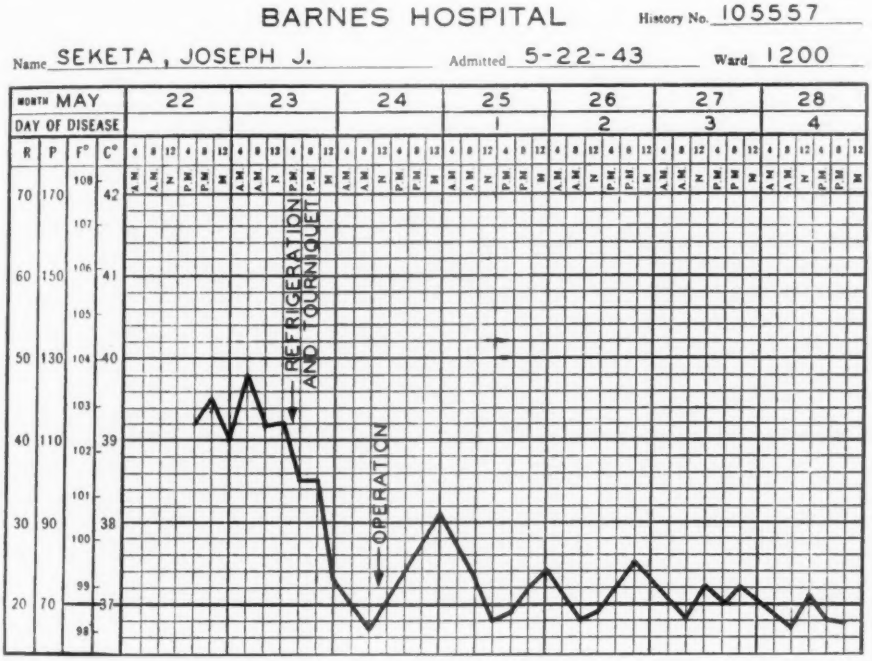

CHART 1.—Case 2: Temperature chart. Note the failure of response to intravenous sodium sulfadiazine and general supportive measures during the first 24 hours of hospitalization, and the marked improvement following refrigeration and the application of a tourniquet.

urine, one plus sugar, numerous W. B. C.; blood sugar 324 mg. per cent; blood N. P. N. 13 mg. per cent. Insulin, whole blood, fluids and sulfadiazine were given. In the evening of the day of admission, ice bags were placed about the right leg and foot almost up to knee level and two hours later a tourniquet was applied to the leg just below the knee. The patient gradually became more comfortable, and within six hours the temperature had fallen to normal. Twelve hours after refrigeration had been instituted, a right midthigh amputation was performed, under spinal anesthesia, without release of the tourniquet. The wound was closed with drainage, and the drain was removed after 24 hours. The postoperative course was uneventful, the wound healed *per primam*. The patient was discharged from the hospital, May 8, 1943, 28 days after admission, in good condition.

Case 2.—J. J. S., a 48-year-old white male, was admitted to the Barnes Hospital, May 22, 1943, and stated that he had had pain in the legs and feet during exercise or in cold weather for six years. A month and a half prior to admission, an area of infection developed about the right great toe; this was treated conservatively, but gangrene of

the toe developed and it was amputated with closure of the stump, elsewhere, eight days prior to admission. Three days before entry the foot became painful, swollen and blue. Pain was so severe that frequent injections of morphine failed to give relief.

Examination showed a critically ill, middle-aged male who frequently dropped off to sleep; his memory was hazy and he was obviously quite toxic. The temperature record is shown in Chart 1. The distal portion of the right foot was gangrenous, and the remainder of the foot up to the ankle swollen, puffy and extremely tender. No arterial pulsations could be felt in the foot, but the popliteal pulse was palpable. Laboratory findings included a W. B. C. of 30,000; and a blood culture was positive for *Streptococcus hemolyticus.*

The patient was given fluids, intravenous sodium, sulfadiazine, and gas bacillus antitoxin, without improvement. Therefore, the day after admission, ice bags were packed around the right foot and leg to just below the knee, and when sensation disappeared, a tourniquet was applied to the leg. Improvement in the general condition was dramatic (see Chart 1), and 24 hours later a circular supracondylar amputation was performed under spinal anesthesia. The wound was closed without drainage. Healing *per primam* followed, and the patient was discharged from the hospital, June 8, 1943, 17 days after admission, in good health.

Histologic study of the amputated tissues confirmed the clinical diagnosis of Buerger's disease, with gangrene of the foot.

Case 3.—M. H., a 19-year-old white female, was admitted to the Barnes Hospital May 26, 1943. She had been knocked off a motorcycle three days before, and a compound fracture of the right ankle sustained; this was treated elsewhere. Spreading infection soon appeared, and the patient was referred to Barnes Hospital for further treatment.

Examination showed an acutely ill, toxic young girl complaining of severe pain in the right leg. The temperature was 38° C. There was evidence of an unreduced fracture of the right ankle, on the lateral side of which was a necrotic, foul-smelling wound from which bubbles of gas could be expressed. The entire right foot and leg were swollen, exquisitely tender, and crepitant, and gas could be felt in the subcutaneous tissues of the thigh as well. Roentgenograms confirmed the diagnosis of gas gangrene.

Large doses of polyvalent gas bacillus antitoxin were administered, the leg was packed in ice up to the level of the knee, and a tourniquet applied. The symptoms rapidly subsided, and, four hours later, under general anesthesia (cyclopropane), a guillotine supracondylar amputation was performed, and several incisions were made over the involved portions of the right thigh. The wounds were left open, and they were irrigated frequently through tubes placed therein. Healing was slow but satisfactory. The patient was discharged from the hospital, July 3, 1943, with all wounds healed.

Case 4.—J. M. L., a 50-year-old white female, was admitted to the Barnes Hospital, November 13, 1943, for removal of an acoustic neuroma on the right side. A meningioma was removed through a cerebellar craniotomy on November 16, 1943. During convalescence the patient, who also suffered from rheumatic heart disease with auricular fibrillation, released an embolus which lodged at the bifurcation of the aorta, and although a large embolus was removed from the left femoral and iliac vessels, November 27, 1943, both legs had to be amputated subsequently just above the knee. On December 4, 1943, a right supracondylar amputation was performed. The patient then developed fever of 39.8° C., and this was thought due to infection in the gangrenous left foot. Accordingly, December 6, 1943, ice packs were applied to the left leg up to the knee, and after two hours a tourniquet applied below the knee. The temperature immediately fell to normal, and 18 hours later, a left supracondylar amputation was performed under general anesthesia (ethylene). The wound was closed without drainage. Postoperative progress was slow, but satisfactory. A slight degree of muscle breakdown occurred and drained out through a small sinus track. This had not healed completely

when the patient left the hospital, January 19, 1944, but did so in about two weeks thereafter.

Case 5.—A. C., a 61-year-old colored male, was admitted to St. Louis Homer Phillips Hospital December 4, 1943. He had fallen out of a second story window one hour previously and was unconscious for some time. Examination showed a deep laceration of the forehead and a severe injury to the right eye, which subsequently developed traumatic cataract. As the patient became more alert, he began to complain of pain in the left leg and foot. The latter was cold, insensitive and paralyzed, and the left popliteal and tibial pulsations were absent. There was a small chip-fracture of the lateral condyle of the left femur.

It was thought that thrombosis in an arteriosclerotic popliteal artery had occurred following direct injury. There was no evidence of an hematoma in the popliteal space. Conservative therapy was tried, but was unsuccessful. Gangrene of the left foot and lower leg gradually developed. There was severe pain and fever as high as 41° C. Accordingly, December 17, 1943, the left leg and foot were packed in ice and a tourniquet applied below the knee. Improvement was dramatic, the temperature shortly falling to 37.6° C. Twenty-four hours later, under spinal anesthesia, a midthigh amputation was performed. The wound was closed over a small rubber dam drain, around which there exuded a small amount of serous fluid which stopped when the drain was removed 48 hours after operation. The wound healed *per primam*. The patient had some fever after operation, but this disappeared when sulfathiazole, which was being administered prophylactically, was discontinued. His subsequent course, as far as the amputated limb was concerned, was entirely satisfactory, although he was kept in the hospital until February 9, 1944, for treatment of his injured eye. Histologic study of the amputated leg confirmed the clinical diagnosis of thrombosis in a sclerotic popliteal artery, with resultant gangrene.

Case 6.—C. B., a colored female, age 57, was admitted to the St. Louis Homer Phillips Hospital December 10, 1943. She had had a partial amputation of both feet for frostbite nine months previously, and had been living in an unheated basement in the interim. Her present complaint was increasing pain in both stumps for some three weeks, following repeated exposures to cold. Examination showed moist gangrene of both stumps, with swelling and tenderness to midleg level on both sides. Conservative treatment was attempted, but the gangrene extended and infection became more marked. The temperature ranged around 39° C. occasionally reaching 40.6° C. Since both popliteal pulsations were good, it was decided to amputate below the knees. On January 10, 1944, both stumps were refrigerated, and tourniquets applied just above the line of demarcation at the ankles. The temperature fell rapidly to normal, and next day bilateral midleg amputations were performed under spinal anesthesia. The wounds were closed, with drainage. There was some sloughing of the skin margins of the lateral aspects of both wounds, and complete healing had not occurred after one month, but the patient's general condition was at all times satisfactory after operation. It was felt that the delayed healing in this case may have been associated with amputation too close to the refrigerated areas.

COMMENT.—Each of the six cases presented had gangrene of one or both feet associated with infection and toxemia. In one instance (Case 2) there was septicemia. The basis for the gangrenous process, as determined by histologic study, was different in each of the cases—diabetic arteriosclerosis, thrombo-angiitis obliterans, spreading gas bacillus infection, peripheral embolism, popliteal thrombosis and frostbite being found. The patients were operated upon without mortality and without encountering difficulty with the subsequent wound healing. It is felt justifiable, therefore, to

advocate the use of the method to others, in order that through wider experience its real merits may be determined.

The details of the procedure used are not complicated. In all but the last case, ice bags were applied nearly up to the knee (Fig. 1) and the tourniquet placed below the knee two to four hours later, after anesthesia had been obtained. When the patient's general condition warranted it, usually after 24 hours, amputation was performed above the knee, using inhalation or spinal anesthesia. Because it is known that living tissues will conduct cold fairly efficiently,[16] and for other reasons already considered, it is important that the amputation be carried out well above the refrigerated area. None of the patients herein reported suffered from shock during or after the operation, an advantage stressed by the proponents of refrigeration anesthesia.

The small number of cases treated by this method does not warrant any sweeping claims. However, refrigeration was not used in any case unless the patient's condition was so poor, due to severe infection and absorption from the gangrenous part, that the ordinary methods of treatment seemed dangerous. Such cases previously have been treated by guillotine amputation, followed by elective amputation at a higher level at a later date. By the method herein employed the necessity for two operations has been obviated.

SUMMARY AND CONCLUSIONS

Refrigeration of an extremity abolishes pain and lessens the blood and lymph flow. When such refrigeration is followed by, and combined with, the application of a tight tourniquet, absorption of toxic products from an infected gangrenous extremity is, for all practical purposes, eliminated.

Because refrigeration tends to delay wound healing and decreases the power of resistance of tissues to bacterial invasion, the prolonged cooling *of tissues to be preserved* is not advocated. It is recommended that necessary amputations be carried out above the level of cooling.

Because a patient's general condition can be improved so greatly, during the combined use of cold and the tourniquet, by ordinary restorative measures, it is unnecessary to avoid the use of inhalation or spinal anesthesia for amputation.

Six illustrative cases cared for in accordance with the above principles are reported.

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EFFECTS OF COOLING ON EXPERIMENTALLY INFECTED TISSUES*

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THE EFFECTS OF REDUCED TEMPERATURES on tissue survival under anoxia and on tissue resistance to infection have been studied in several recent investigations. Allen,[1] and Brooks and Duncan,[2] showed that cooling greatly prolongs the life of tissues deprived of their blood supply. The experiments of Brooks and Duncan[3] also have demonstrated, conclusively, that the local application of cold without interference with the blood supply prevents the development of the normal tissue response to bacterial organisms ("*Staphylococcus aureus*") and to chemical irritants (turpentine) injected intracutaneously, and that the appearance of the classical signs of inflammation rapidly follows the return of the affected part to a normal environmental temperature.

In this communication are reported the results of an investigation to determine the effects of reduced temperatures on both the local tissue response and the organisms responsible for it, and to determine the eventual course of a local infection as altered by a temporary period of cooling.

EXPERIMENTAL PROCEDURE

A concentrated suspension of "*Streptococcus hemolyticus*" in broth was used to produce a localized infection. The suspension was obtained from 18-hour cultures, and bacterial counts showed its concentration to vary within the range of 10^8 to 10^9 in all specimens.

Mongrel dogs weighing from four to eight kilos were used as experimental animals. After the hair was removed from one of the forelegs, 0.5 cc. of the suspension was injected into the wrist joint or into the subcutaneous tissues above the wrist. The inoculated limbs were then cooled to six degrees C. for various lengths of time. Cooling was effected by immersing the limb to a level well above the elbow in a constant temperature bath provided by a commercial cooler. The dogs were immobilized in canvas hammocks and the affected limb in the cooler was made secure by a tie placed well below the wrist. This insured the uninterrupted cooling of the limb and did not interfere with the blood supply to the inoculated area. No protective substances were applied to the skin, and food and water were not withheld from the animals during the course of the experiment. The control animals

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the office of Scientific Research and Development and Washington University, St. Louis, Mo.

were injected in a similar fashion and were placed in cages at room temperature for equivalent periods of time, no effort being made to immobilize the inoculated limb. These experiments were carried out for periods ranging from 24 to 96 hours. Each experiment was performed on two groups of six dogs. In the first group, the gross and microscopic structure of the lesions was studied, and bacterial counts were made from samples of the exudate. This method of securing material for counts was found to be in-

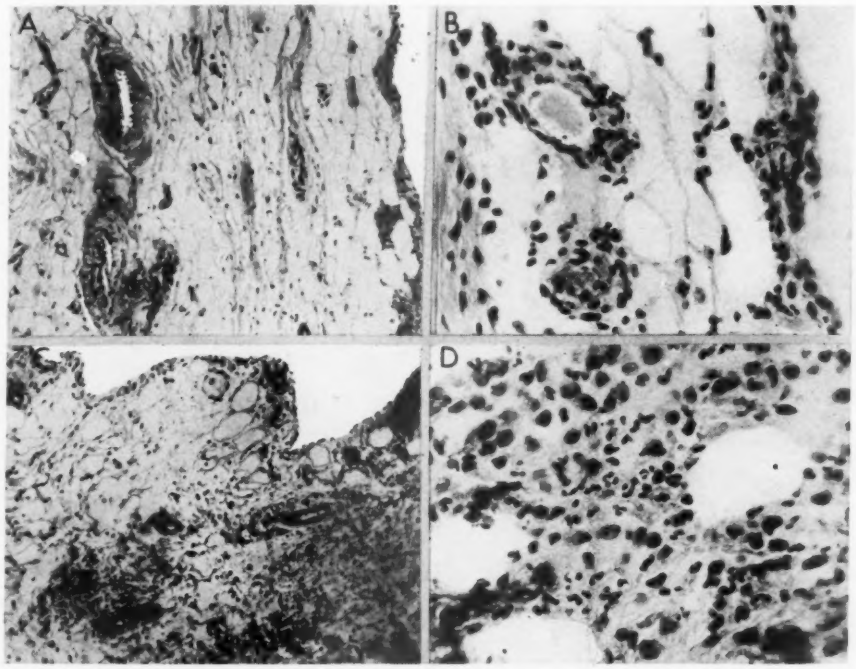

PLATE I.—A. Photomicrograph (× 135) of the synovial membrane of a dog's wrist joint inoculated with *"Streptococcus hemolyticus"* and cooled at 6°C. for 48 hours.
B. Photomicrograph (× 425). Same as A, to show more clearly the vascular congestion and minimal degree of leukocytic infiltration.
C. Photomicrograph (× 135) of the synovial membrane of a dog's wrist joint inoculated with *"Streptococcus hemolyticus"* and maintained at room temperature for 48 hours.
D. Photomicrograph (× 570). Same as C, to show more clearly the slight degree of acute inflammatory response exhibited in the joint synovial membrane of the control dog.

accurate—so that a second group of animals was prepared in which at the completion of the experimental cooling, the tissues at the site of inoculation were excised *"en bloc,"* care being taken that the excision extend well out into normal tissue. These specimens were then homogenized and the total number of bacteria per sample determined. The controls were carried out similarly in two groups of six animals for each experiment.

All bacterial counts were determined by dilutions in broth poured over blood agar plates and are expressed in number of bacteria per cubic centimeter. Contamination was very infrequent, and the organisms recovered were invariably identified as *"Streptococcus hemolyticus."*

EXPERIMENTAL RESULTS

The effect of local cooling on infected subcutaneous tissues was studied for periods of time varying from 24 to 96 hours.

In a first experiment dogs were inoculated subcutaneously with 0.5 cc. of the bacterial suspension. In one group the limbs were cooled for 48 hours immediately following the injection, and the animals were then sacrificed. The other group was left at room temperature for the same period of time before being studied.

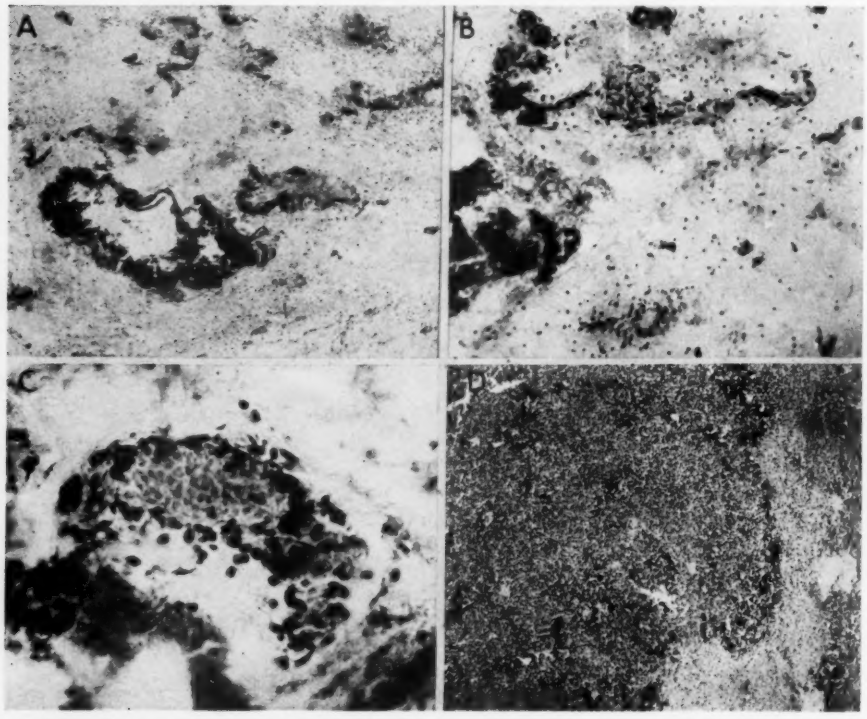

PLATE II.—A. Photomicrograph (× 50) of the subcutaneous tissue of a dog's limb at the site of inoculation after cooling 48 hours at °C. Note the presence of vascular congestion and edema without appreciable leukocytic infiltration around the dark ring of bacteria embedded in the tissues.

B. Photomicrograph (× 135) from the same area as A to show the relatively acellular edema and minimal diapedesis.

C. Photomicrograph (× 570) from the same area as A showing a distended capillary near a cluster of bacteria (lower part of picture). Note the absence of tissue reaction to the bacteria.

D. Photomicrograph (× 50) of the subcutaneous tissues of a dog's leg at the site of inoculation with *"Streptococcus hemolyticus"* after 48 hours at room temperature. Note the marked acute inflammatory reaction.

In the limbs that had been subjected to cooling there was no external evidence of inflammation at the site of inoculation. Local anesthesia and local loss of motor function were noted in all animals. At autopsy, on gross examination, diffuse edema, though of varying degree, was found to be present in all cases throughout the area that had been immersed and to involve mostly the subcutaneous layer. The edematous tissue had a greyish-blue color and a viscid, gelatinous consistency. Around the site of injection, these greyish tissues assumed a faint pinkish color. Closer examination of

the area showed a fine reddish reticulum suggestive of dilated blood vessels. Gross extravasation of blood was not observed.

Even away from the site of inoculation, there was microscopic evidence of marked vascular congestion and edema. Around the congested capillaries one could see a few polymorphonuclear and red blood cells. These findings were also observed in the subcutaneous tissues of animals that had been submitted to cooling without any bacterial inoculation. In the inoculated area the vascular dilatation was more marked and the diapedesis, although minimal, was somewhat more marked, also. Only a few inflammatory cells were observed however, at any distance from the capillaries and the edematous tissue was remarkably free of cellular infiltration. In many sections large clumps of bacteria were seen embedded in the tissues, without any evidence of cellular activity around them (Plate I, A, B and C). The bacterial counts performed on the exudate fluctuated widely but were all considerably lower than the original counts of the bacterial suspension injected.

The control animals, at room temperature, all showed a well-defined external swelling at the site of inoculation with redness of the skin in a few instances. At autopsy, on gross examination, a small cutaneous abscess was found in all animals. The microscopic picture was characteristic of an acute inflammatory reaction with abscess formation (Plate I—D). The purulent material obtained from the abscess yielded bacterial counts that varied widely, but were definitely higher than those obtained from the animals subjected to cooling. On the basis of subsequent evidence obtained in this research, it is clear that the method employed for obtaining the samples of exudate was defective. The difficulty with which only minute amounts of fluid could be obtained from the edematous cooled tissues repeatedly necessitated resorting to washings, and the clumping observed in the microscopic sections suggested that variable counts could probably be obtained from different parts of the same specimen.

To eliminate these objections the experiments were repeated on other animals. The same procedure was followed but after the completion of the experiment the inoculated tissues were excised widely and the counts made from this whole specimen.

This procedure was first carried out over a period of 24 hours. The number of bacteria recovered from the tissues subjected to cooling was only slightly lower than that injected (Table I). The counts obtained from

TABLE I

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER LOCAL COOLING AT 6°C. FOR 24 HOURS

No. of Dog	Bacterial Counts Per Cc.	
	Suspension	Tissue
43A	5.9×10^8	2×10^8
45A	5.9×10^8	2×10^7
11C	4.9×10^8	1×10^8
6C	4.9×10^8	9×10^8
20C	7.8×10^8	4.6×10^8
15C	7.8×10^8	1.8×10^8

the controls though consistently high, were lower than those obtained from the cooled tissues and lower than the original number injected (Table II).

The bacterial counts obtained after 48 hours of cooling were substantially the same as those observed after 24 hours of cooling (Table III). The controls showed a further reduction in the number of bacteria, the

TABLE II

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER 24 HOURS AT ROOM TEMPERATURE

No. of Dog	Bacterial Counts Per Cc.	
	Suspension	Tissue
37A	5.9×10^8	6×10^7
40A	5.9×10^8	1.6×10^7
9C	4.9×10^8	1×10^7
2C	4.9×10^8	2×10^6
22C	7.8×10^8	1.3×10^8
18C	7.8×10^8	2.4×10^7

TABLE III

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER LOCAL COOLING AT 6°C. FOR 48 HOURS

No. of Dog	Bacterial Counts Per Cc.	
	Suspension	Tissue
44A	5.9×10^8	1.7×10^8
41A	5.9×10^8	4×10^7
8C	4.9×10^8	2.5×10^8
7C	4.9×10^8	1.5×10^8
26C	8.9×10^8	2.8×10^8
23D	8.9×10^8	1.6×10^8

TABLE IV

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER 48 HOURS AT ROOM TEMPERATURE

No. of Dog	Bacterial Counts Per Cc.	
	Suspension	Tissue
38A	5.9×10^8	4.5×10^4
42A	5.9×10^8	8×10^6
3C	4.9×10^8	8.1×10^7
1C	4.9×10^8	1.7×10^6
25D	8.9×10^8	1.5×10^6
27D	8.9×10^8	2.4×10^5

counts being lower than those obtained after 24 hours in untreated animals, and markedly lower than the original number of bacteria (Table IV). In both these experiments, the gross appearance of the tissues showed the characteristic changes previously described.

Similar experiments were then carried out with the period of cooling extended to 96 hours. The aspect of the cooled tissues was similar to that found after 48 hours. The amount of subcutaneous edema however, and the vascular congestion were usually greater. In these animals after block excision of the tissues, the number of bacteria recovered approximated roughly the number injected (Table V). In the controls, abscess formation was a constant finding. In many animals, after the required period of time at room temperature, the abscess had ruptured through the skin. A large number of animals had, therefore, to be inoculated before we could obtain six

tissue specimens with an intact skin. The bacterial counts obtained from these tissues were much lower; showing that in this time period the local defense mechanisms had overcome the infecting organisms to a marked degree (Table VI).

TABLE V

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER LOCAL COOLING AT 6°C. FOR 96 HOURS

	Bacterial Counts Per Cc.	
No. of Dog	Suspension	Tissue
9E	8.7×10^8	1.8×10^8
11E	8.7×10^8	1.9×10^8
12E	8.7×10^8	4.3×10^8
14E	$6.6 \quad 10^8$	5.4×10^8
15E	6.6×10^8	6.6×10^8
16E	6.6×10^8	4.2×10^8

TABLE VI

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER 96 HOURS AT ROOM TEMPERATURE

	Bacterial Counts Per Cc.	
No. of Dog	Suspension	Tissue
26C	6.3×10^8	1.0×10^3
48C	6.3×10^8	1.4×10^3
47C	6.3×10^8	3.4×10^5
5E	3.0×10^8	8.0×10^3
6E	3.0×10^8	2.6×10^5
7E	3.0×10^8	1.0×10^3

The experimental method was then modified to determine the effects of a return to a normal environment after a preceding period of cooling. Groups of animals were inoculated according to the same technic, and cooling applied to the limb for a period of 48 hours. The animal was then removed from the cooler and left at room temperature for an additional period of 48 to 96 hours. The limbs warmed up very rapidly following removal from the cold bath. Within 48 hours after discontinuing the application of cold, the edema of the limb would disappear, leaving a localized swelling at the site of injection. The results of the examination of this area, in the gross, were very similar to those observed in animals left at room temperature for 48 hours after inoculation. But in most of the animals which had been subjected to a period of cooling the area of inflammatory changes was slightly greater than in the controls. In none, had the abscess broken out through the skin but in some instances, superficial necrotic lesions of the skin were noted. Microscopically, there was a typical acute inflammation that could not be differentiated from that observed in the controls except for the subjective impression that the amount of edema was slightly greater. The bacterial counts obtained from the excised tissues showed a decrease from the original number of bacteria injected and approximated those observed in animals after 48 hours at room temperature without previous cooling (Table VII).

When 96 hours were allowed to elapse after cooling had been discontinued, the individual variations in the gross appearance of the lesion

were greater than in any of the previous experiments. A localized abscess was observed in all cases. While in some instances, the area of inflammation was slightly smaller than that observed after 48 hours, in others it was larger than any observed in the controls after 96 hours. This wide variation was also noted in the bacterial counts obtained from the excised tissues (11 dogs). In some animals the number of bacteria recovered showed only a slight decrease or no change at all; in others, the counts showed a marked decrease over the number of bacteria originally injected (Table VIII).

TABLE VII

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER LOCAL COOLING FOR 48 HOURS FOLLOWED BY 48 ADDITIONAL HOURS AT ROOM TEMPERATURE

No. of Dog	Bacterial Counts Per Cc. Suspension	Tissue
27C	6.3×10^8	5.8×10^7
23C	6.3×10^8	1.4×10^5
29C	6.3×10^8	1.8×10^8
4D	5.1×10^8	3.9×10^6
3E	3.0×10^8	4.8×10^4
4E	3.0×10^8	4.3×10^5

TABLE VIII

NUMBER OF BACTERIA IN THE SUSPENSION INJECTED AND IN THE EXCISED TISSUES AFTER LOCAL COOLING FOR 48 HOURS FOLLOWED BY 96 ADDITIONAL HOURS AT ROOM TEMPERATURE

No. of Dog	Bacterial Counts Per Cc. Suspension	Tissue
1F	8.0×10^8	3.4×10^5
2F	8.0×10^8	1.1×10^5
3F	8.0×10^8	8.3×10^8
4F	8.0×10^8	3.7×10^8
5F	7.2×10^8	3.7×10^4
7F	7.2×10^8	2.6×10^3
8F	7.2×10^8	3.9×10^3
23G	2.1×10^9	4.2×10^6
24G	2.1×10^9	4.8×10^6
28G	2.1×10^9	1.6×10^9
29G	2.1×10^9	1.0×10^9

Finally, another series of experiments was carried out with the site of inoculation at a greater distance from the surface. In spite of the small bulk of the limb, the wrist joint seemed best suited to this purpose. The joint was inoculated with 0.5 cc. of the bacterial suspension. One group of animals was treated by local cooling and the other left at room temperature for periods of 24 and 48 hours.

The control animals did not show, grossly, as severe an acute pyogenic arthritis as had been expected. There was some congestion of the synovia and minute amounts of turbid fluid in the joint. The recovery of "*Streptococcus hemolyticus*" from this fluid, however, established the fact that the joint had been inoculated. Microscopic examination of the capsule showed an acute inflammatory reaction but not of the intensity of that observed in the subcutaneous infections (Plate II, C and D).

In the animals which had been refrigerated the gross appearance of the

limbs was not greatly different. The microscopic sections showed only minimal reactive changes (Fig. II, A and B). The bacterial counts obtained from the joint exudate showed the same trend as those reported after subcutaneous injections.

COMMENT.—The exposure of inoculated tissues to a temperature of 6° C. for periods up to 96 hours results in a definite inhibition of the usual inflammatory response to "*Streptococcus hemolyticus*" encountered in the control animals. This inhibition is evidenced by the gross and microscopic picture

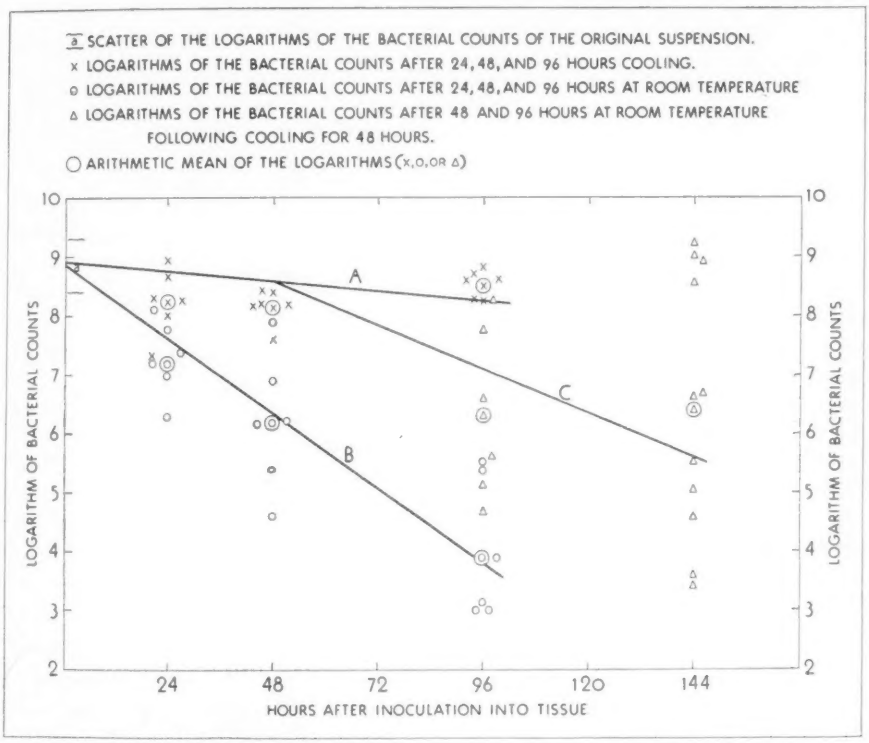

CHART 1.—A. Curve showing that during cooling the number of bacteria in the tissues remains relatively unchanged.
B. Curve showing the decrease in the number of bacteria in the tissues which occurs at room temperature.
C. Curve indicating the tendency for bacteria to disappear more slowly from the tissues when a period of cooling has preceded the return to a normal environmental temperature.

observed after cooling. It is further substantiated by the fact that no significant decrease in the number of organisms injected is observed under these conditions. At room temperature, the decrease in the number of bacteria follows a logarithmic curve. A comparison of these data (Chart I) indicates that cooling delays markedly the rate of destruction of bacteria in living tissue, in spite of the inhibition of growth which probably takes place at low temperatures *in vivo* as well as *in vitro*. In these experiments no attempt was made to determine the proportion of bacteria that had spread to the regional lym-

phatics or that was carried away by the blood stream. Gelatinous edema, vascular congestion and minimal diapedesis were noted throughout the cooled limb, even at a distance from the site of inoculation. The degree of edema seemed related to the length of the cooling period. Finally, these changes were also observed in limbs that were cooled without any previous inoculation. This would suggest that some of the reactive changes observed in the tissues are due to the effects of cold itself. As the limbs were immobilized in a dependent position, dependency could be regarded as an additional factor, although it alone did not produce this lesion. It is noteworthy that this edema, with temporary anesthesia and loss of motor function and the occasional appearance of necrotic skin lesions after the return of the limb to a normal environment, bears a striking resemblance to the clinical syndrome of immersion foot. At the site of inoculation, the pathologic findings were similar but slightly more marked. At the same depth at which these slight reactive changes were found clusters of bacteria without any inflammatory cells around them could be observed. The short, but inevitable, time-lag necessary to reduce the tissue temperature to an adequate level may also be partly responsible for these findings. The evidence seems to indicate that the application of cold in itself for periods up to four days will not have a beneficial effect on the course of a localized infection. At most, a relative *status quo* is present as long as the reduced temperature is maintained. However, the constant finding of diffuse edema in our experiments argues against regarding this condition as a merely innocuous suspension of bacterial and tissue activity.

Brooks and Duncan reported that the area of necrosis which appeared after cooling had been discontinued, was larger than if the lesion developed at body temperature. In their investigation, they were able to study both lesions in the same animal. In our experiments a return, after cooling, to a normal environmental temperature resulted, also, in a grossly more severe inflammation, although the microscopic picture was not significantly different from that observed in the controls. As the lesion under study and the control had to be produced in different animals, individual variations made an exact quantitative comparison difficult. Inasmuch, as the rate of destruction of bacteria after a previous period of cooling will give some measurable indirect evidence of the alteration of tissue response by cold, Chart 1 shows that the trend under these conditions is towards a slower rate of destruction than that observed under normal conditions. The scatter of individual variations in the experiments where cooling had been resorted to widens as the elapsed time increases, and precludes the plotting of an accurate curve. Insofar, as is shown by our data, there is reason to believe that the growth restricting action of the tissues is somewhat decreased by cooling. Statistical studies on a very much larger group of animals may be necessary to substantiate this finding.

The inoculation of joints did not measure up to our expectations as an

experimental procedure. Our findings did show, however, that the effects of cooling are manifest even in the deeper structures in spite of their constant perfusion by warm blood. In the human, Bierman[4] reported a drop of 10° to 25° F. one and one-half inches from the surface of the calf when cold had been applied externally for one or two hours. In their experiments Brooks and Duncan noted the appearance of some reactive changes in the subcutaneous tissues while none were observed at the site of the intradermal inoculation. They concluded that this is an indication of the relatively small depth of temperature alteration by external applications. However, their method of cooling differed greatly from that used in these experiments as they applied cold only to the very limited area of injury. This discrepancy between our results and those reported by Brooks and Duncan would seem to lie in the procedure used rather than in the process itself. The temporary anesthesia and loss of motor function which follows cooling also provides supportive evidence that the deeper structures as well as the superficial were affected.

From these experimental data, it seems evident that the clinical application of cold (6° C.) to infected tissue will have no therapeutic value in itself. Under certain circumstances, it may not be harmful to cool an infected limb for a brief period in order to maintain the relative *status quo* observed in these experiments in regard to bacterial activity and to tissue response. However, under our experimental conditions, cooling for longer periods of time (24 to 96 hours) resulted in definite changes in tissue hydration, in marked vasodilatation and in a decrease in the growth restricting action of tissues towards bacterial organisms. Moreover, these changes became more marked as the period of refrigeration was prolonged. While the exact clinical limitations of the procedure remain to be determined, this would contraindicate, except for brief periods, the cooling to levels around 6° C. of infected limbs which one aims to save by conservative measures.

SUMMARY

As long as cooling to 6° C. is maintained, the subcutaneous tissues of the dog fail to show the inflammatory response usually initiated by the innoculation of "*Streptococcus hemolyticus.*" The number of organisms present in the tissues remains remarkably constant and closely approximates the number injected.

The development of extensive subcutaneous edema during cooling and after removal of the cold, the development of a more marked inflammatory reaction, with a decrease in the growth restricting power of the tissues to bacterial organisms, suggest the possibility of harmful effects from prolonged refrigeration.

The effects of cooling are manifest in the deeper as well as in the superficial tissues of the limb of a dog with an intact blood supply.

The clinical implications of the above results are discussed briefly.

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THE EFFECT OF COOLING ON WOUND HEALING*

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GENERAL CONSIDERATIONS

The velocity of many biologic processes varies directly with the temperature. This relationship is expressed in the temperature coefficient (Q 10) of such processes, which designates the ratio of the rate of the process at one temperature to that at another 10° C. lower, and frequently follows van't Hoff's law for chemical reactions by falling somewhere between two and three.[1] In some instances, experimental data obtained in studying certain processes, such as velocity of growth, have been found to show changes with temperature with sufficient consistency to permit an expression of the relationship between the two in the form of a mathematic equation.[2] In general, it can be stated that the velocity of most biologic processes is retarded by lowering and speeded-up by elevating the temperature. For example, the rate of division of unicellular organisms (*ameba proteus*) is retarded by lowering the temperature within limits of 4° to 30° C., and is completely inhibited at 4° C.;[3] fibroblasts cultured *in vitro* show maximum growth at 39° C., the rate diminishing with decrease in temperature, and no growth occurring at or below 20° C.[4] More specialized tissues, such as nerve exhibit, a decrease in activity with lowering of the temperature. Conduction time is prolonged, refractory period is lengthened, and the potential associated with conduction is diminished in amplitude.[5] The highly intricate process of metabolism in man is known to vary directly with changes in body temperature, the basal metabolic rate varying some 13 per cent with each degree centigrade change in temperature.[1]

The effect of temperature change on pathologic processes, such as inflammation, has been less thoroughly studied. It is well known that the growth of bacterial organisms is depressed by lowering the temperature, but it is important to remember that in most instances bacteria can be kept alive for long periods at temperatures of 5° to 10° C. without being damaged or destroyed,[6] whereas, prolonged cooling of an extremity of any of the higher animals or man leads to certain harmful effects on the tissues.[7, 8] Brooks and Duncan[9] recently studied intradermal infections in animals following cooling and noticed certain harmful effects both during and after the cooling period. Bruneau and Heinbecker[10] investigated the effects of cooling on subcutaneous and intra-articular infections in dogs. They found that the inflammatory response of the tissues was inhibited during the

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Washington University School of Medicine.

period of cooling and exaggerated when normal temperatures were re-established, and that the growth restricting power of tissues to bacterial organisms was inhibited by prolonged cooling. They also noticed that lowering the temperature of a dog's leg for some time produced edema, loss of sensation, and partial or complete paralysis.

The effect of temperature change on the healing of wounds has not been investigated, to our knowledge, although the processes involved in wound healing itself have been studied thoroughly. Among the more important biologic phenomena concerned are ameboid movement, mitotic proliferation, and the maturation of cells. Since these processes have been studied separately, and, in general, have been shown to exhibit velocities varying directly with the temperature, it seems reasonable to assume that wound healing would be adversely affected by lowering the temperature of the part. The present study was undertaken to investigate this problem, with the hope that the results might serve as a basis for determining the indications for the use of refrigeration in clinical surgery. It can be stated that the results observed are such as would have been expected logically to follow from available scientific evidence.

EXPERIMENTAL DATA

Materials and Method: In principle, the experiments performed were quite simple; one of the animal's forelimbs was cooled for a period of from 24 to 72 hours, and the manner in which wounds of the skin and subcutaneous tissue healed was observed; an incision in the opposite uncooled forelimb was used as control. The experiments may be conveniently separated into two series, with three groups comprising the first series, and two, the second.

Series 1—Group A.—Mongrel dogs weighing from four to eight kilograms were used as experimental animals. The hair was removed from the lateral side of the forelegs, using sodium sulphide as depilator, and the animals were lightly anesthetized with intravenous sodium nembutal. The skin was prepared with iodine and alcohol, and longitudinal incisions, five to six centimeters in length, through the skin and subcutaneous tissue of both lower forelegs, were made with a sharp knife. Hemostasis was secured by pressure, and the skin edges were then approximated without tension by means of interrupted fine silk sutures seven to eight millimeters apart. Thin rubber condoms were next placed over both forelimbs and sutured in place high up on the body, care being taken to see that no constricting effect was present. The animals were then placed in canvas hammocks arranged so that one forelimb was immersed to elbow-level in water maintained by means of a commercial cooling apparatus at a constant temperature of 6° C. (with limits of 4° to 8° C.) and immobilized there by a tie placed well below the level of the incised area. The other limbs, including the control limb, were immobilized sufficiently to keep the animal within the apparatus, but not completely to prevent movement of the hind limbs. In this way,

the incised forelimb was exposed to cold for a period of 48 hours, without the cold water actually coming into contact with the wound (for exceptions, see later). During this time the animals' food and water intake was unrestricted. After the prescribed cooling period the dogs were removed from the apparatus, the condoms were taken off and the animals returned to their cages. They subsequently were killed at varying intervals, the wounds studied histologically and estimations of their tensile strength made.

The sutures were removed on the seventh day, or before the wounds were studied. The tensile strength was measured in grams per centimeter wound length, by a simple clamp or hook and weight-bearing device, an average of two or three determinations being used for each of the computations; cross-sections of the wounds were fixed in formalin, embedded in paraffin, and stained with hemotoxylin and eosin for microscopic examination.

Series 1, Group B.—These animals were treated in a manner similar to those in Group A, except that the period of cooling was maintained for only 24 hours.

Series 1, Group C.—These dogs, after having some of the hair of the forelimbs removed with clippers, were placed in the cooling apparatus without condoms over the forelimbs, for 72 hours. They were then anesthetized and incisions made in both forelimbs, and immediately sutured. The animals then were returned to their cages and wound studies performed at varying intervals as in Groups A and B.

Series 2.—In the second series of experiments an attempt was made to study the effect of cooling on wounds treated by delayed suture.

The forelimbs were prepared as before, incised, and sterile dressings applied. Rubber condoms were fixed in place over the forelimbs, and the animals placed in the cooler for 24 or 48 hours. On removal from the cooler, the animals were again lightly anesthetized, the dressings removed, the skin around the wound prepared again, and the incisions closed with interrupted fine silk sutures. In Group A of this series the cooling period was 24 hours, in Group B, 48 hours. The wounds were studied at varying intervals by gross examination, by microscopic section and by estimation of tensile strength as in Series 1.

RESULTS

Series 1, Group A.—Gross infection of the wounds occurred in a considerable percentage of cases. The results from such animals are not included in the estimations of tensile strength. In certain instances the rubber condoms broke, or the animals' struggles allowed water to splash into the container, so that the cold water was in direct contact with the wound. Healing in this minority of cases seemed similar to that which occurred in those remaining perfectly dry, and it was, therefore, decided that in this particular series it would be permissible to include these results with the others. The tensile strengths of all the wounds which healed cleanly are

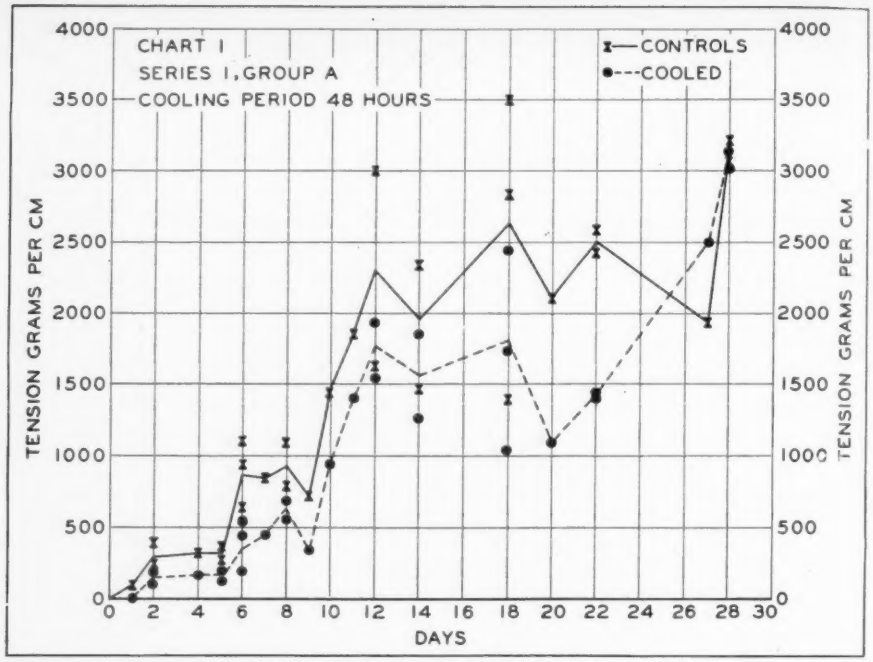

CHART 1.—Tensile strength measurements of wounds during the healing period. "X" marks the average tensile strength of one control wound in Gm/cm., and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

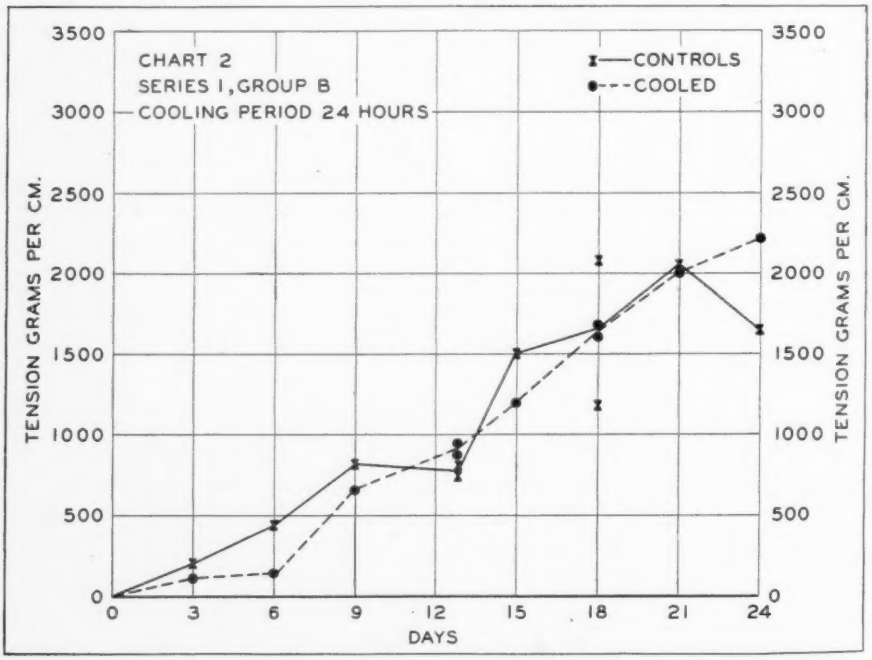

CHART 2.—Tensile strength measurements of wounds during the healing period. "X" marks the average tensile strength of one control wound in Gm/cm., ad "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

given in Chart 1. A total of 55 dogs was studied in this group, but 28 of them had to be discarded because of disease or infection. The chart, thus, depicts the relative strength of 54 wounds in 27 dogs during various phases of the healing period.

These results may be compared with Charts 2 and 3, which give the results of those experiments in which cooling was performed for 24 and 72 hours, Groups B and C of this series, respectively. Although these latter experiments were done on smaller numbers of animals, the results are sufficiently uniform to be useful for purposes of comparison.

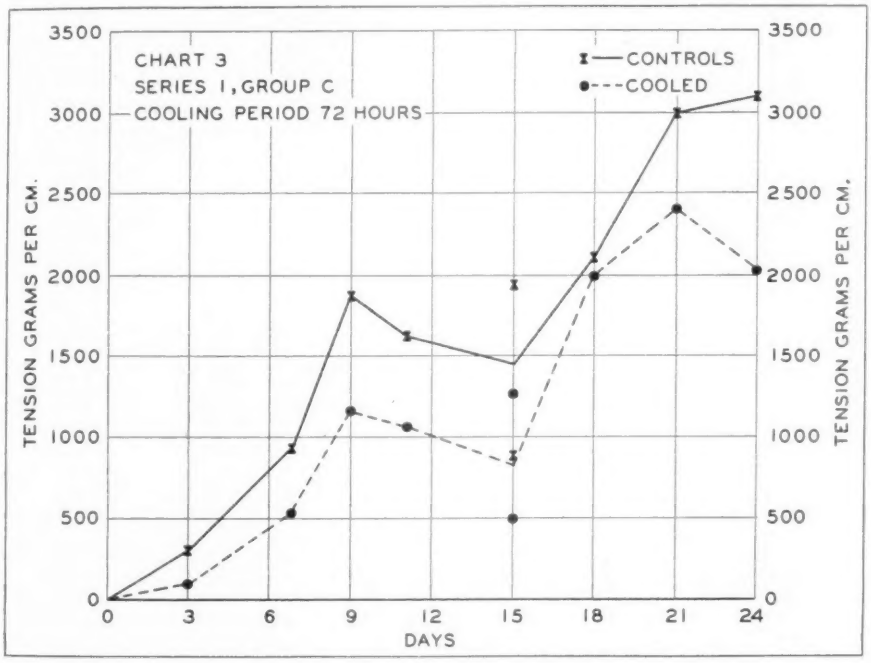

CHART 3.—Tensile strength measurements of wounds during the healing period. "X" marks the average tensile strength of one control wound in Gm/cm., and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

The histologic appearance of the healing wounds in these experiments varied considerably (Fig. 1-4). The incidence of infection in the 72-hour group was high; four of a group of nine dogs showed definite evidence of infection of the refrigerated wounds, while only one of the controls became infected. In all three groups the wounds not infrequently displayed some microscopic widening or infiltration with inflammatory cells, even though no gross evidence of infection was present. Otherwise, the healing process, as evidenced by histologic findings, seemed to parallel the charted estimations of tensile strength. It is noteworthy that sections of the incisions taken immediately after cooling showed no microscopic evidence of tissue

response to the injury, whereas beginning healing was evident in the controls (Fig. 1).

Series 2.—The results obtained in the second series of experiments, where the limb was incised, then cooled, and sutured after the cooling period, were difficult to assess from the point of view of clean healing. Only those results were included in which the wounds remained dry, without leakage or tearing of the protective rubber envelope. In Group A

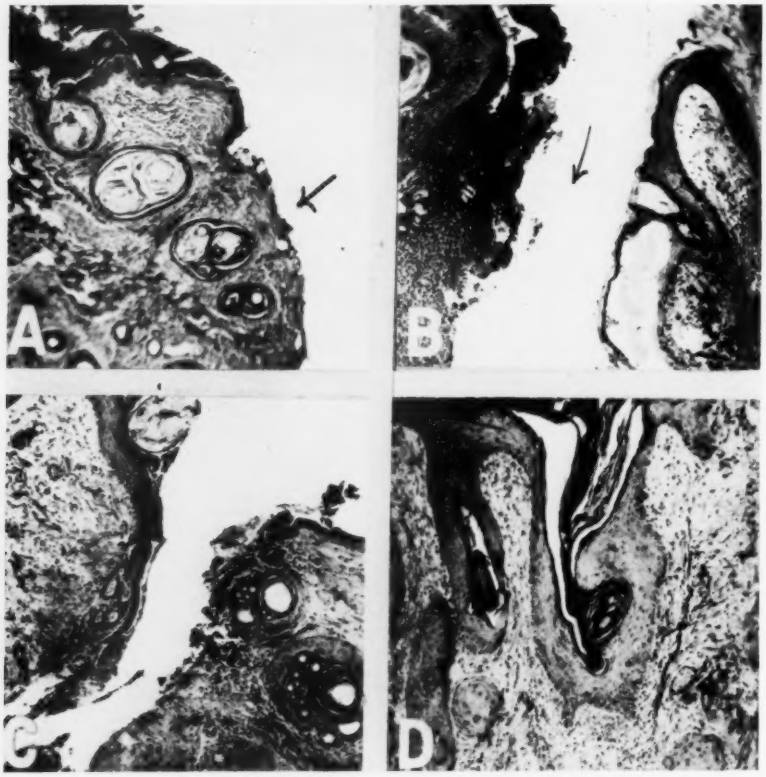

FIG. 1.—Photomicrographs (×60) of tissues stained with hematoxylin and eosin, from Series 1, Group A, in which the cooling period was 48 hours.

A and B. Sections of wounds immediately following the cooling. An arrow designates the wound edge in each. Note absence of reaction in cooled wound A, with exudate of inflammatory cells and fibrin in control B.

C and D. From dogs three days after the cooling period. Note slight cellular reaction in the cooled wound C, epithelization with beginning fibroplasia in control D.

(cooling period 24 hours) six of the nine dogs used developed gross infection of the wound in the cooled limb, while only two of the controls became infected. However, the infected wounds healed rapidly, once the pus had been discharged, both in the cooled and control limbs. Tensile strength in such wounds, as modified by the frequent presence of infection, are given in Chart 4. Histologic studies confirmed the evidence of gross infection in each case (Fig. 5). In the second group of this series, Group B (cooling period 48 hours) the results were similar but more marked. Of

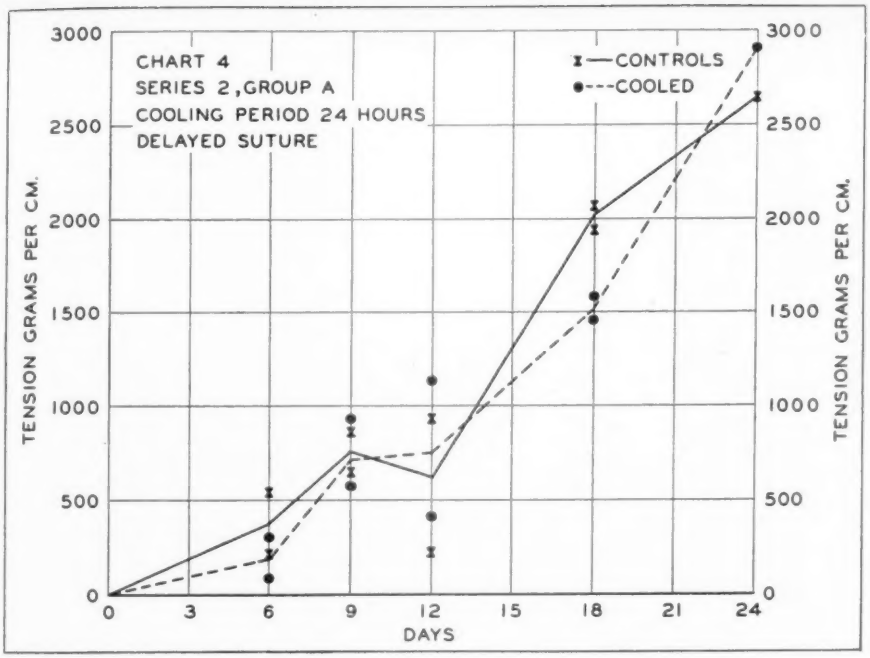

CHART 4.—Tensile strength measurements of wounds during the healing period. "X" marks the average tensile strength of one control wound in Gm/cm., and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

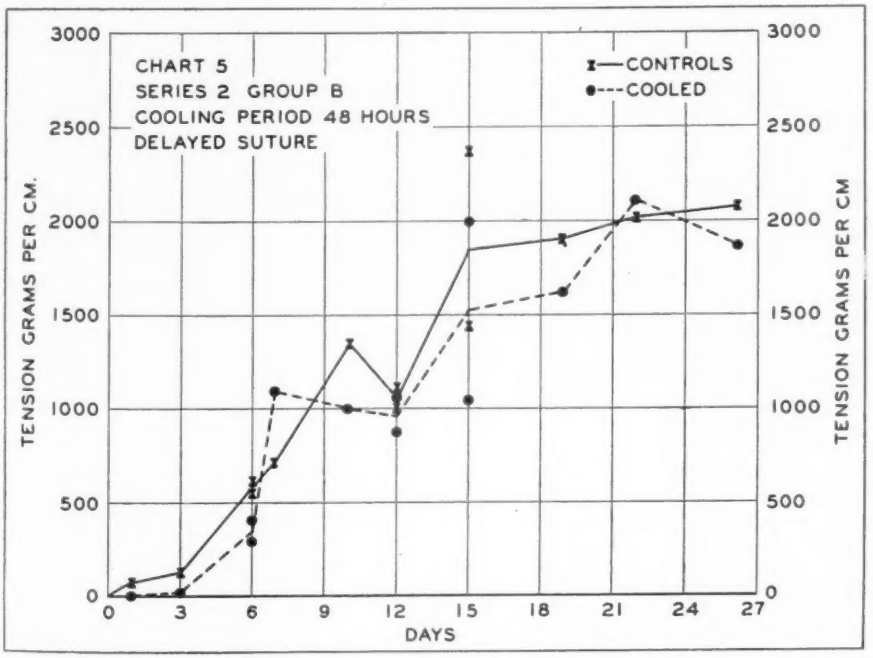

CHART 5.—Tensile strength measurements of wounds during the healing period. "X" marks the average tensile strength of one control wound in Gm/cm., and "O" the average strength of a cooled wound. Where more than one animal was killed at any particular time during the healing process, the curve is drawn through the averaged value of the individual determinations.

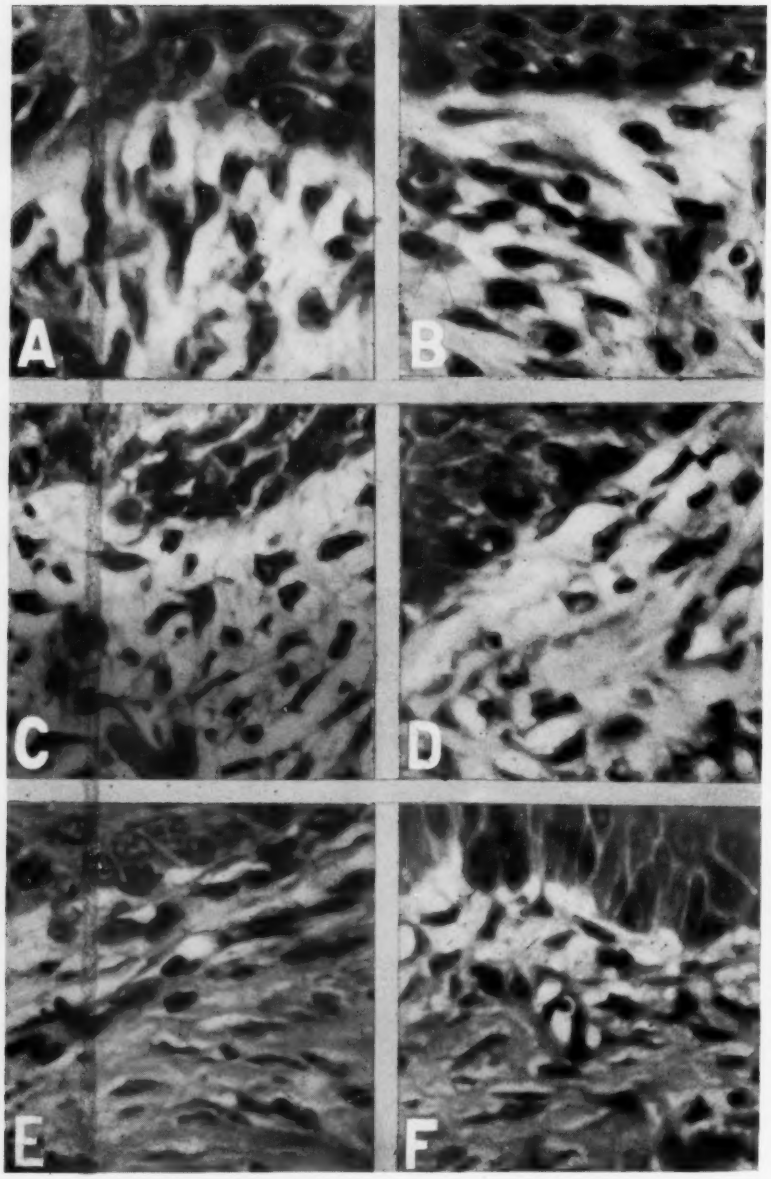

FIG. 2.—Photomicrographs (×575) of tissues from Series 1, Group A, in which the cooling period was 48 hours.

Sections marked A, C and E from cooled wounds, those marked B, D and F from corresponding controls. A and B, 6 days, C and D, 8 days, E and F, 12 days following the cooling period. Note slightly greater edema, less regularity of fibroblasts and poorer deposition of collagen in the cooled wounds.

13 dogs used, nine of the incisions in the cooled limbs and only one of the control wounds became infected. The tensile strengths of these wounds are given in Chart 5. Histologic confirmation of infection, again, found in every case, is shown in the photomicrographs of Figure 6.

Another significant feature was noticed in this latter series of experiments. When the animals were removed from the cooler and the dressings taken off, the uncooled control incision showed pinkish, firm beginning granulations, whereas, the cooled limb appeared as it had when incised 24 or 48 hours previously.

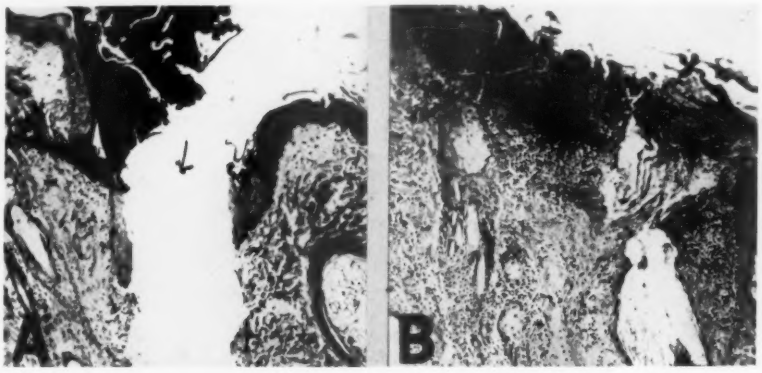

FIG. 3.—Photomicrographs (×60) of tissues from Series 1, Group C, in which the cooling period was 72 hours.
A and B. Sections taken three days after cooling. Note absence of reaction and hemorrhage on the surface of the cooled wound A. An arrow indicates the wound area.

DISCUSSION.—The results of the first series of experiments permit a comparison of the healing process in cooled with that in uncooled limbs. They show (1), that during the cooling period there is no response to the trauma of the incision; (2), that for any given period during the healing process the cooled incisions exhibit a delay in healing, as evidenced by measurements of tensile strength, (3), that when cooling is prolonged (48 to 72 hours) the lag in healing is most marked late in the course of the healing process; and (4), that the degree of delay in healing is roughly proportional to the duration of the cooling period (Chart 6). It is significant that cooling a limb for two days results in sufficient damage to the tissues to cause a marked effect on wound healing for more than two weeks after the actual cooling period.

The results of the second series of experiments show that prolonged refrigeration of a wound followed by delayed suture results in a higher incidence of infection than would have been the case if cooling had not been used. The high incidence of infection in those wounds made and sutured after cooling the limb for 72 hours (Series 1, Group C) indicates that very prolonged refrigeration results in greater risk of infection, even if the wounds are sutured immediately. It is interesting that this increased incidence of infection in cooled incisions gives direct confirmation to the

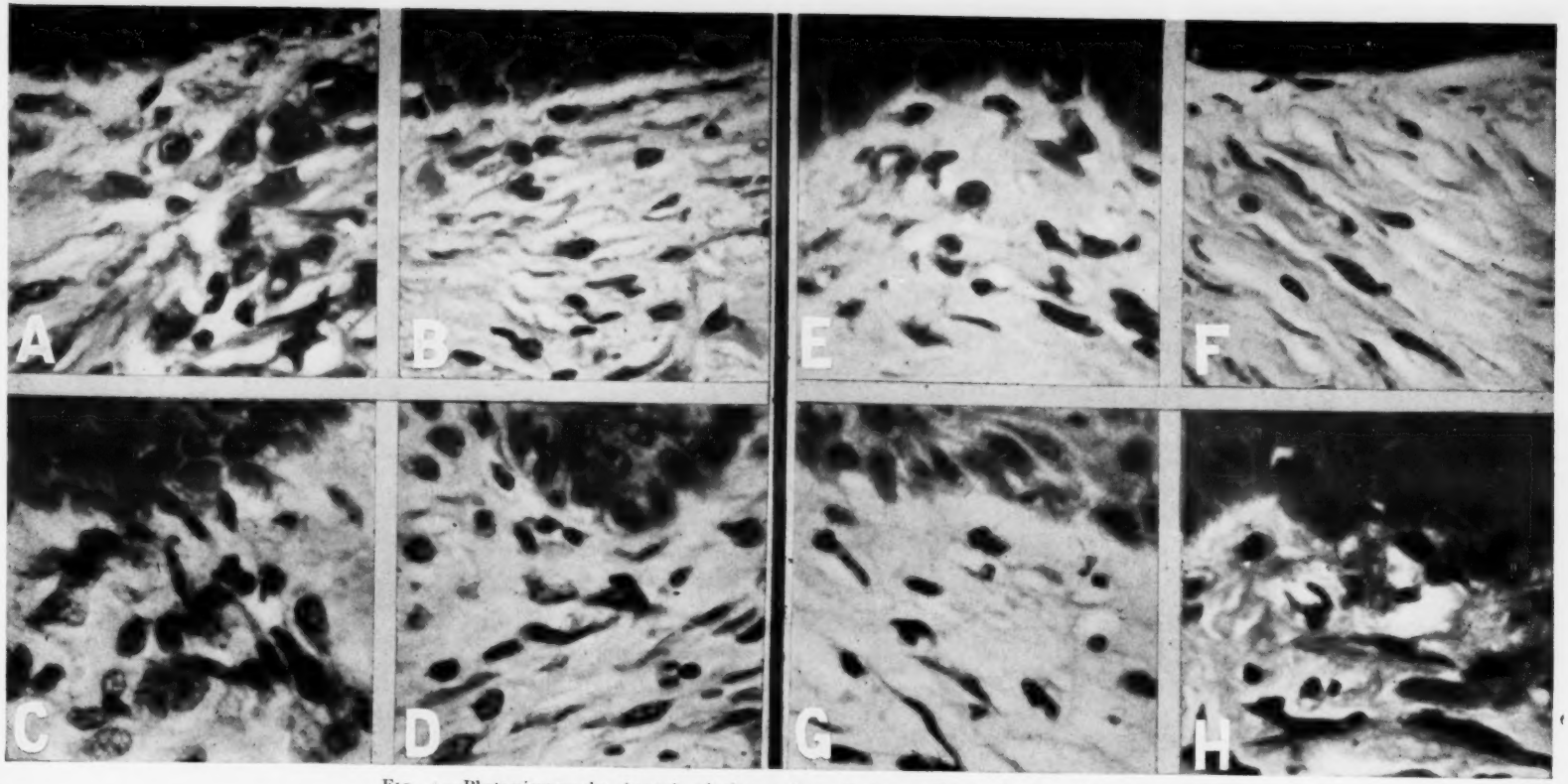

FIG. 4.—Photomicrographs (× 575) of tissues from Series 1, Group C, in which the cooling period was 72 hours.

A, C, E and G from cooled wounds; B, D, F and H from corresponding controls. A and B, 9 days, and D, 11 days, E and F, 15 days, G and H, 21 days following cooling. Note that the wounds in cooled tissues show irregular growth and immaturity of the fibroblasts. The amount of collagen formed is less. Note that the degree of retardation of wound healing is more marked than in comparable wound cooled for 48 hours. (Fig. 2).

work of Brooks and Duncan[9] and of Bruneau and Heinbecker,[10] who found, as already mentioned, that prolonged refrigeration of contaminated or infected tissue results in certain harmful after effects.

The mechanisms involved in the production of the harmful effects on wound healing following refrigeration merit further comment. For although inhibition of the healing process would be expected to occur during the cooling period, in accordance with the known retardation of biologic processes at lower temperatures, the extent of the damage was actually found

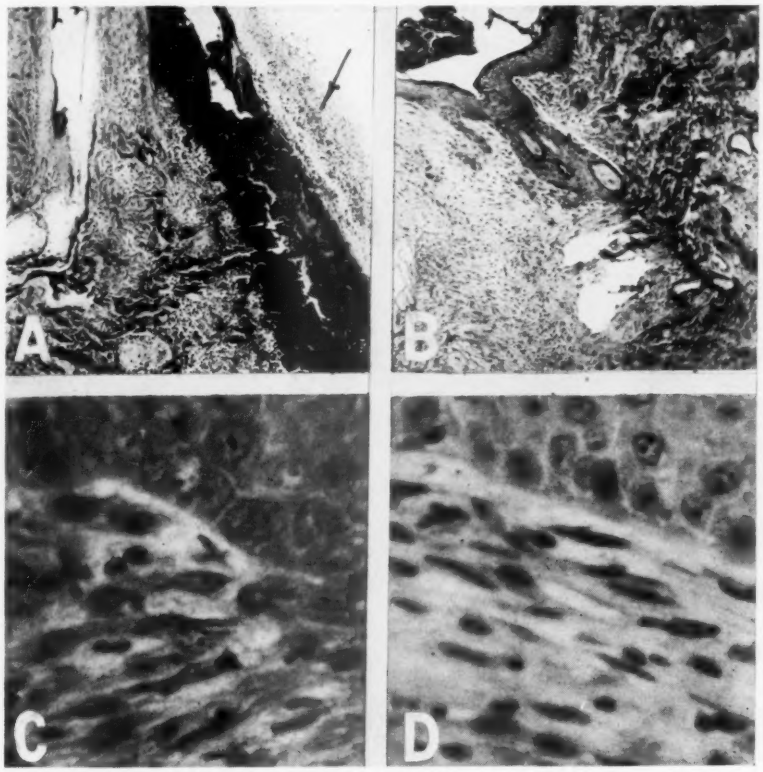

FIG. 5.—Photomicrographs of tissues from Series 2, Group A, in which delayed suture following cooling for 24 hours was performed.
A and B (× 60), 6 days after suture. The cooled wound A is wide open and ulcerated. The control B is healing with considerable fibroplasia.
C and D (× 575), 12 days after suture. The fibroblasts are large and less mature and there are more inflammatory cells in the cooled wound C than in the control D.

to be much greater after the cooling agent had been removed. An explanation of these findings is revealed by an analysis of the local factors known to influence wound healing. These include, (1), the amount of killed or damaged tissue in the wound surfaces; (2), the integrity of the blood flow to the damaged tissues; this determines the nutrition and viability or the necrosis of the tissues bordering on the wound surfaces, (3), the amount and character of the exudate in the wound space and in the tissues

bordering the wound; (4), the number and character of pathogenic organisms in the wound space and bordering tissues; and (5), the number and character of foreign bodies to be extruded or encapsulated.[11] In our experiments the amount of damaged tissue and the number of pathogenic organisms and foreign bodies (sutures) were constant for control and cooled limbs. There remain for consideration the integrity of the blood

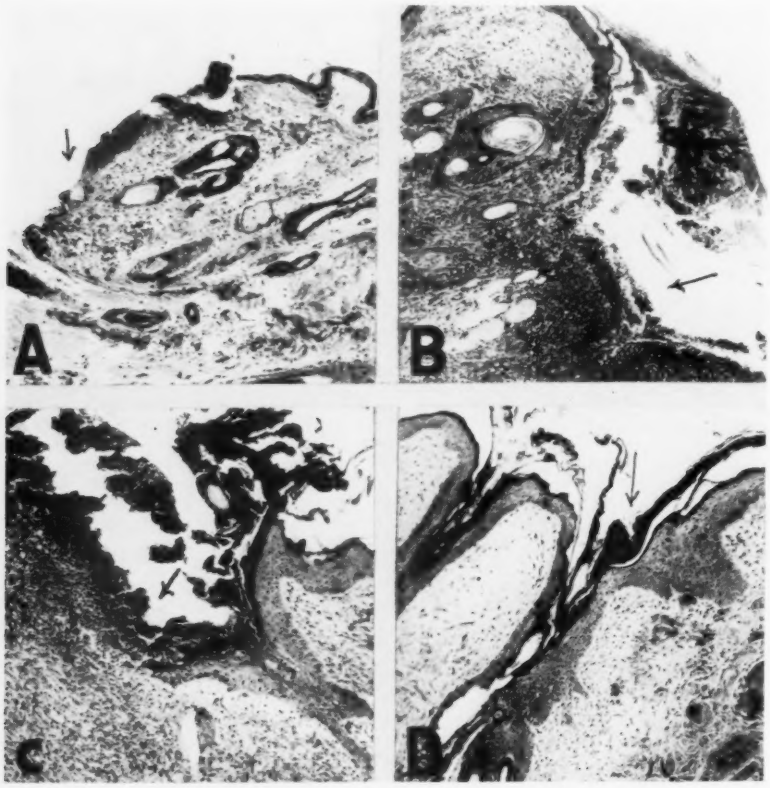

FIG. 6.—Photomicrographs (×60) of tissues from Series 2, Group B, in which delayed suture following cooling for 48 hours was performed. An arrow designates the wound in each section.

A and B, directly after cooling; there is no reaction in the cooled wound A, marked exudation in the control B.

C and D, 6 days after cooling and suture. The cooled wound C is wide open and ulcerated, the control D is healing cleanly.

flow to the part and the amount and character of the exudate formed. Lowering the temperature of the involved tissues changes both of these latter factors in a manner tending to delay wound healing and to promote bacterial growth. For it is known that prolonged cooling of an extremity results in decreased blood flow through the part and in the production of interstitial edema.[8] The deficiency of blood supply and the edema often remain long after the temperature has been restored to normal, and this accounts for the prolonged derangement of wound healing. A further contributing factor may be trophic changes associated with degeneration of the

peripheral nerves, which has been shown to occur after prolonged exposure of an extremity to cold.[12]

CLINICAL IMPLICATIONS

The results of our experiments, together with those of Bruneau and Heinbecker, indicate that certain harmful effects result from prolonged refrigeration of living tissue, such as is advocated by some for amputation of gangrenous infected extremities. It may be held that, because the duration of the cooling period as applied clinically is often much shorter than that

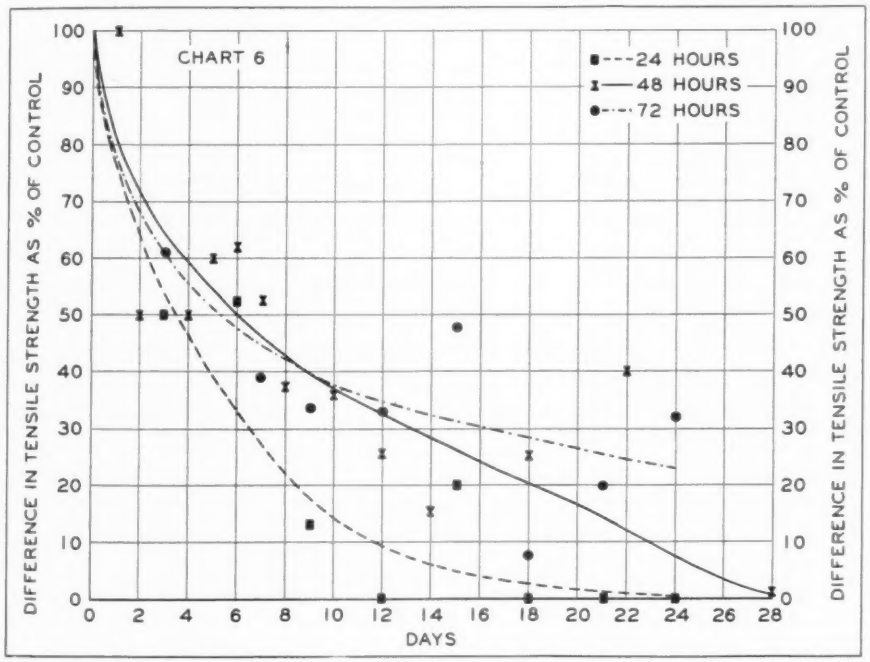

CHART 6.—The difference in tensile strength measurements between cooled and control wounds, plotted as percentages of the controls. They indicate the degree of delay in healing for any given period during the healing process. The data are obtained from Charts 1, 2 and 3, and are plotted as scatter diagrams, the curves occupying mean positions.

Since healing does not occur during the cooling period, the discrepancy between cooled and control is 100 per cent immediately after cooling. It gradually approaches zero over a period of three or four weeks. Note that the 72-hour curve overlaps the 48-hour curve early in the period of healing, a consequence of the fact that the incisions for the 72-hour group were made *after* the cooling period, while those of the 48-hour group were made *before cooling*. In effect, then, the incisions in the 48-hour controls had a two days' start in healing.

employed in these experiments, the results are not comparable. Since it has been shown that the harmful effects are proportional to the duration of the cooling period, it may be assumed that some degree of harm must result whenever living tissues are cooled to low temperatures. It is felt, therefore, that refrigeration anesthesia is not ideal for amputations. If the aim is to diminish absorption from a gangrenous region by local cooling, this can be accomplished by refrigerating the limb below the desired amputation level in order that the anesthesia so induced will permit the appli-

cation of a tight tourniquet. After restorative measures have been effective, amputation then can be carried out under ordinary anesthesia above the level of cooling without harmful sequelae.

Suggestions have been advanced recently by Crossman, Allen, *et al.*,[13] McElvenny,[14] and others, that wounds of the extremities incurred on the battlefield be refrigerated during transportation and until proper emergency surgical treatment can be instituted, an interval of many hours or even days. Our experiments dealing with the effect of prolonged cooling on wounds treated by delayed or secondary suture fairly closely approximate such war conditions. Because of the increased incidence of wound infection after the cooling period shown to occur in these experiments, it is recommended that wounds sustained on the battlefield should not be treated by refrigeration unless there is no hope of saving the part.

SUMMARY

Experiments were carried out on dogs to study the effects of prolonged refrigeration on wound healing. The nature of the healing process in clean incised wounds of the skin and subcutaneous tissues of the forelimb after cooling to 6° C. for a period of 24 to 72 hours was determined, using similar incisions in the opposite limb as controls. The healing process was studied by measurements of the tensile strength and by microscopic examination of the wounds at varying intervals. The results show that during the cooling period there is no reaction on the part of the tissues to the injury inflicted by the incision, and that subsequently there is a definite lag in the healing of the wounds, the degree of delay varying with the duration of the cooling period. In wounds treated by delayed suture after cooling for 24 or 48 hours the incidence of infection is much greater than in control incisions maintained at normal temperatures.

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NERVE DEGENERATION FOLLOWING PROLONGED COOLING OF AN EXTREMITY*

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IN THE COURSE OF RECENT STUDIES on the effect of refrigeration on infection[1] and on wound healing,[2] it was noticed that many of the animals used in the experiments exhibited findings in their extremities similar to those of "immersion foot." The purpose of this communication is to report certain changes found in the peripheral nerves following prolonged cooling.

METHOD

Small mongrel dogs weighing four to eight kilograms were used as experimental animals; 20 of them were used in the experiment. The hair of the forelimbs was partly removed with clippers and the animals were suspended in canvas hammocks so that one forelimb was immersed to approximately elbow level in cold water thermostatically maintained at a temperature of 6° C. The limbs were immobilized by tape ties over gauze wrapped around the wrists and ankles, and the animals were kept in the apparatus for 96 hours, during which time their food and fluid intake was not restricted. They then were returned to their cages and were sacrificed after varying intervals, up to three months following exposure; but before death the threshold to faradic stimulation of the ulnar nerves in the forelimbs was determined. After sacrifice, the superficial anterior and deep ulnar nerves from the cooled limbs were stained with osmic acid, and impregnated with silver according to the technic of Davenport.[3] Sections of the other tissues, including skin, subcutaneous tissues, vessels and muscles were fixed in formalin, embedded in paraffin, sectioned at 5 microns, and stained with hematoxylin and eosin. Corresponding sections from the tissues of the opposite uncooled forelimbs served as controls.

RESULTS

Swelling of the involved limb and partial or complete loss of sensation and paralysis usually were present on removal from the cooler, these signs gradually subsiding over a period of several days. The signs were less marked in well nourished animals, evidently because they moved about more while in the apparatus. The threshold for muscle response to faradic stimulation of the ulnar nerve of the involved limb increased until the fifth day after cooling, when, in most instances a response no longer was obtained on maximal stimulation. The threshold then decreased gradually until about

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Washington University School of Medicine.

the 16th day after cooling, when it was again normal, remaining so thereafter.

Slight histologic changes only were demonstrable in the skin, subcutaneous tissues and muscles. A measure of edema involved all the tissues, including the intermuscular planes, and the walls of the smaller blood vessels, but there were no infiltrations of inflammatory cells. After the edema had subsided, no

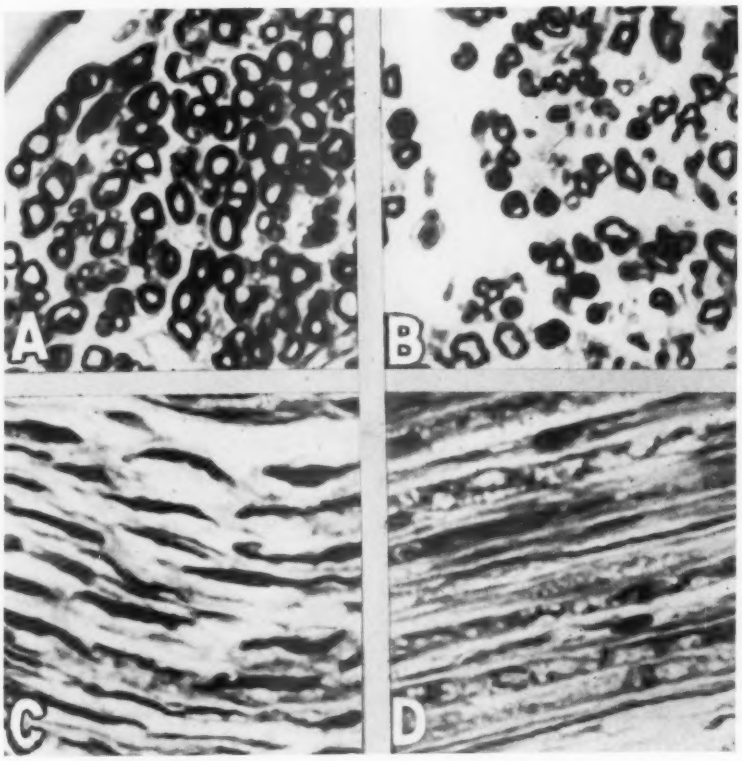

FIG. 1.—Photomicrographs (× 575). Five days after cooling.
A. Cross-section of normal nerve stained with osmic acid. B. Same of cooled nerve. Note beginning fragmentation and disappearance of myelin.
C. Longitudinal section of normal nerve stained with silver. D. Same of cooled nerve. Note marked swelling, fragmentation, and vacuolization of axis cylinders.

difference between cooled and control limbs could be detected microscopically, except for questionable slight fibrosis of the derma and of the subcutaneous tissues.

Contrasted with these minimal findings were the marked degenerative changes noted in the nerves of the cooled area. Swelling of the nerve trunks accompanied the generalized edema of the limb and persisted longer, the cooled nerve trunk often being twice the diameter of the control for ten days, or more, after exposure. Both superficial and deep nerves were involved, the former possibly slightly more than the latter. The microscopic sections revealed varying degrees of wallerian degeneration, as evidenced by frag-

mentation and disappearance of the myelin sheaths, and in certain instances, by swelling, vacuolization and fragmentation of the axis cylinders. These histologic changes were evident five days after cooling, and progressed slowly thereafter, some degree of nerve damage being demonstrable for the entire duration of the experiment (*i.e.*, up to three months after exposure). In most of the nerves studied, the degeneration was patchy in character, but seemed to involve large myelinated, small myelinated, and nonmyelinated

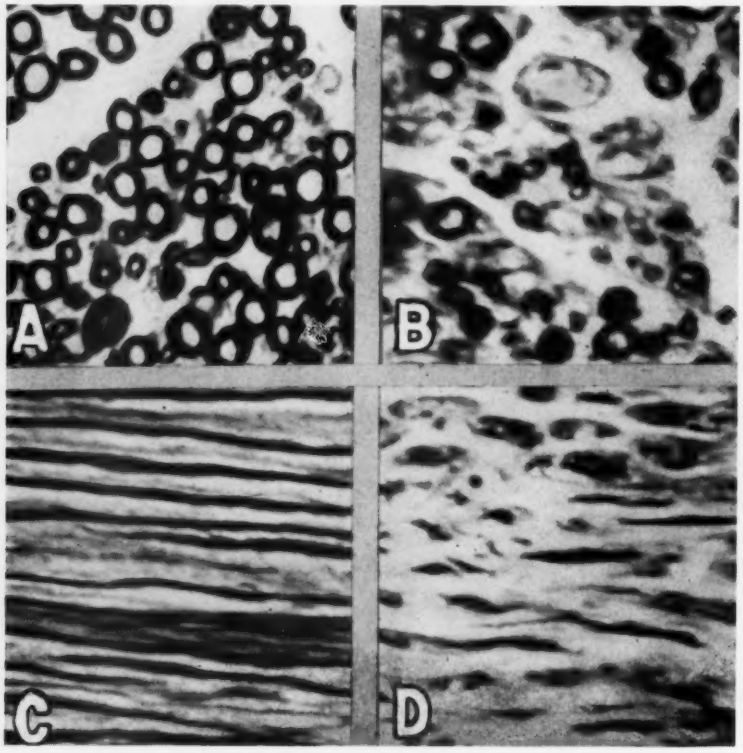

FIG. 2.—Photomicrographs (× 525). Nine days after cooling.
A. Cross-section of normal nerve stained with osmic acid. B. Same of cooled nerve. Note progression of demyelination.
C. Longitudinal section of control nerve stained with silver. D. Same of cooled nerve. Note fragmentation of axones.

fibers to an almost equal legree. Illustrative sections are shown in the accompanying figures. As would be expected, the extent of nerve damage was found to vary directly with the amount of edema and paralysis of the limb following cooling, but organic changes of some degree were present in the nerves invariably even in those instances where no gross evidence of edema or paralysis had been discernible at any time.

DISCUSSION.—The mechanism of production of the changes observed following cooling of an extremity is of interest. The finding of degeneration of the nerves without concomitant inflammatory changes in the other tissues favor the commonly held view that relative ischemia of the part, rather than

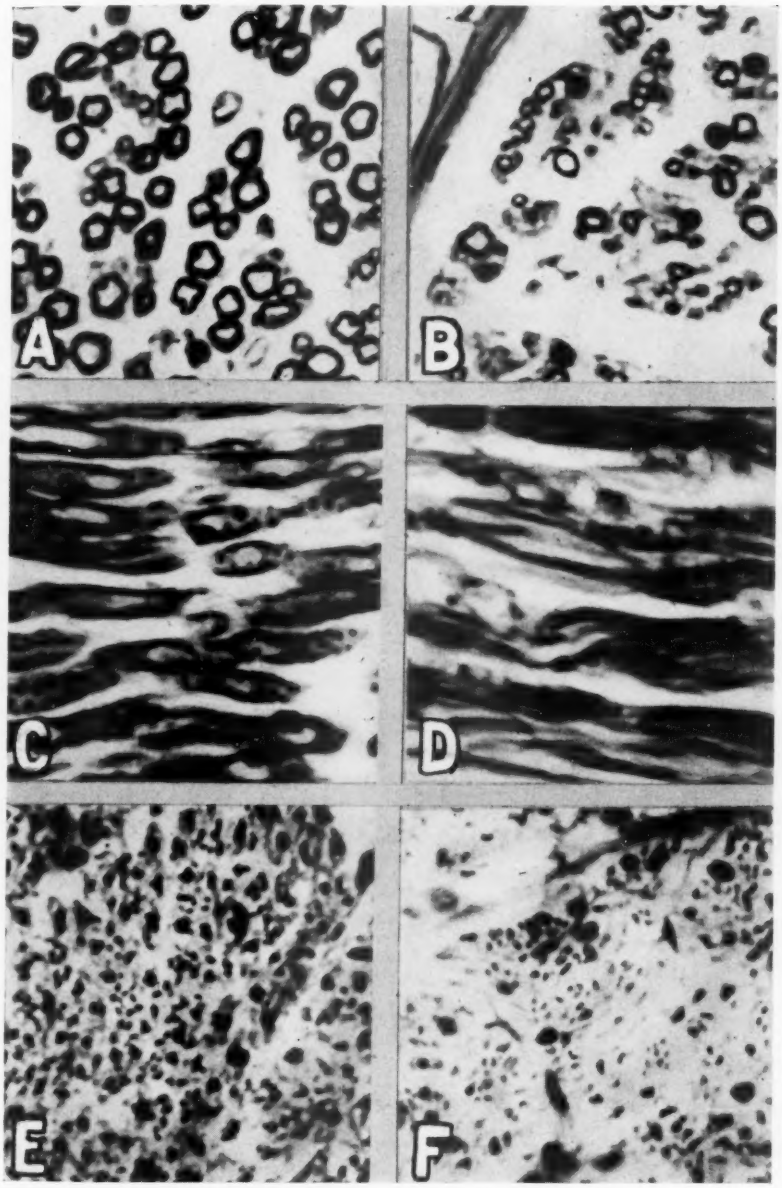

FIG. 3.—Photomicrographs (× 525). Sixteen days after cooling.
A and C. Cross-section and longitudinal section of normal nerve stained with osmic acid. B and D. Same of cooled nerve. Note demyelination.
E. Cross-section of normal nerve stained with silver. F. Same of cooled nerve. Note disappearance of axones.

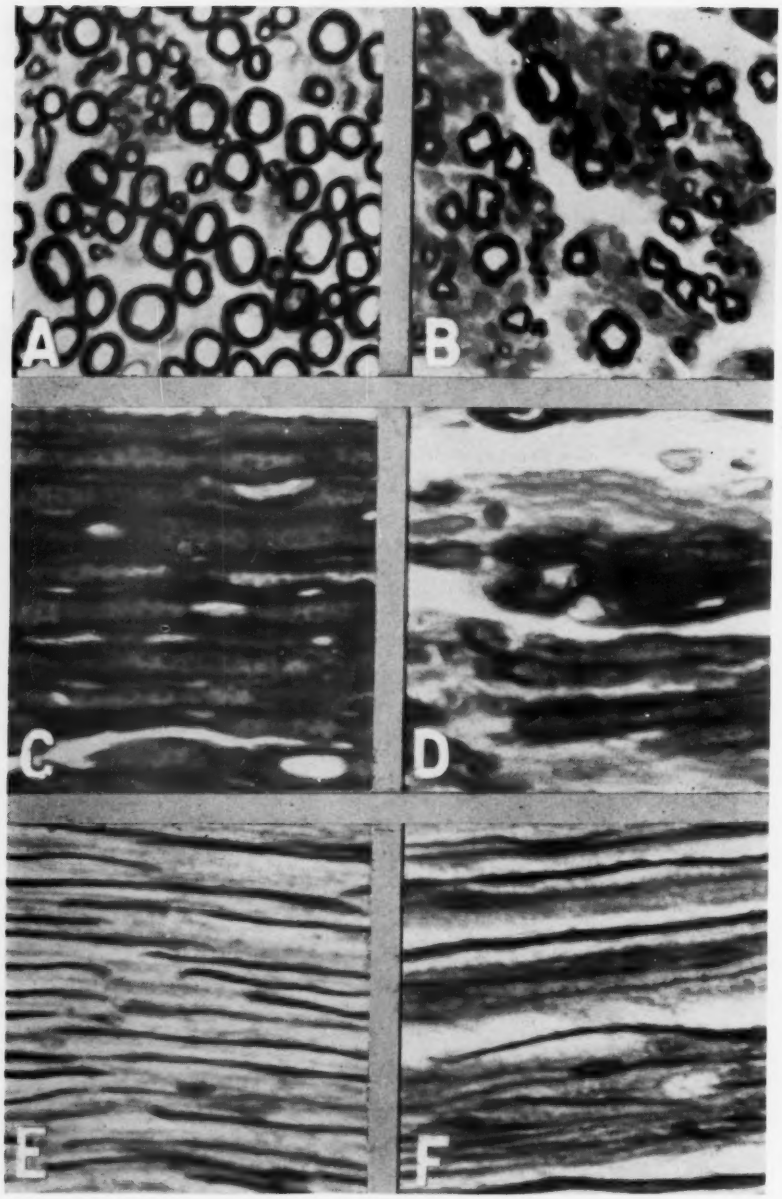

FIG. 4.—Photomicrographs (× 525). Thirty-one days after cooling.
A. and C. Cross and longitudinal sections of normal nerve stained with osmic acid. B. and D. Same of cooled nerve. Note demyelination.
E. Longitudinal section of normal nerve stained with silver. F. Same of cooled nerve. Note that some of the axones have disappeared completely.

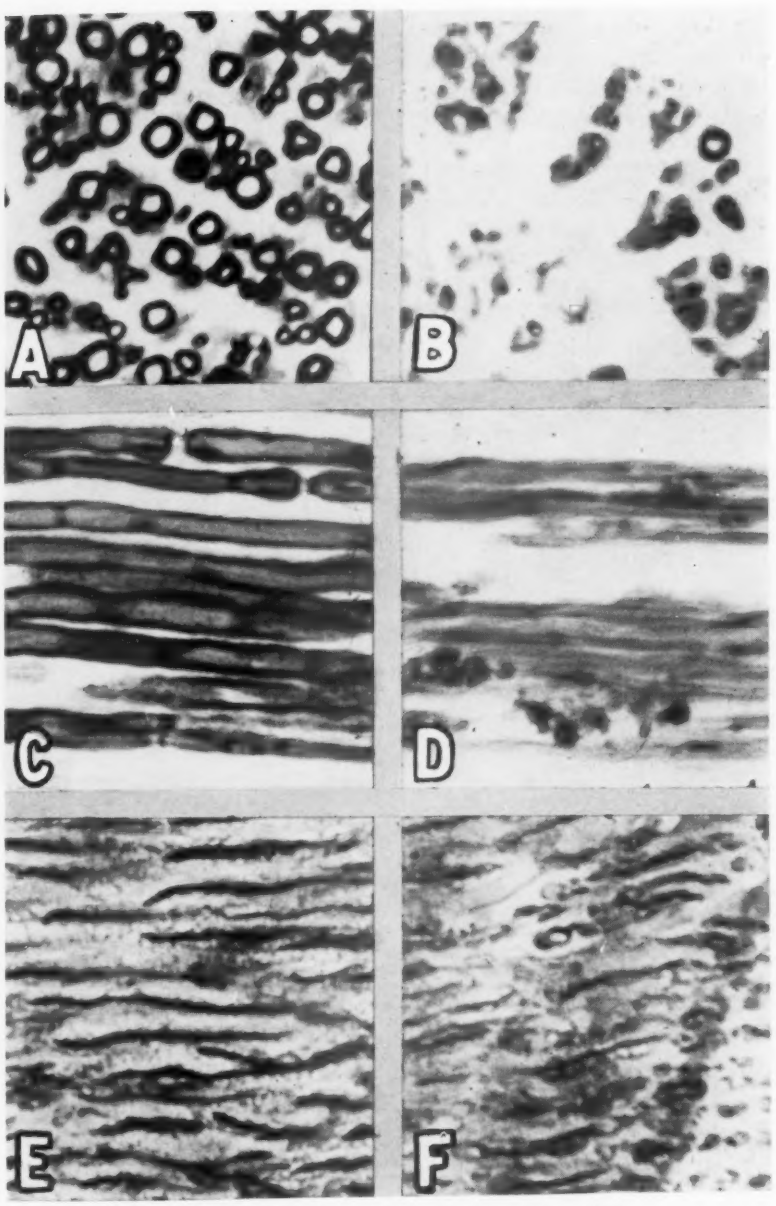

FIG. 5.—Photomicrographs (× 525). Forty-three days after cooling.
A. and C. Cross and longitudinal sections of normal nerve stained with osmic acid. B. and D. Same of cooled nerve. Note almost complete disappearance of myelin.
E. Longitudinal section of normal nerve stained with silver. F. Same of cooled nerve. Note that most of the axones show marked degeneration. This animal's leg exhibited the most marked swelling and paralysis of the entire group.

direct injury of the tissues by cold, is responsible for the damage. This explanation is substantiated by the knowledge (a) that cooling results in prolonged sustained arteriolar constriction,[4] thus decreasing blood flow through and oxygenation of the part; and (b) that local anoxia results in marked increase in capillary permeability,[5] this latter factor thus also accounting for the edema which develops.

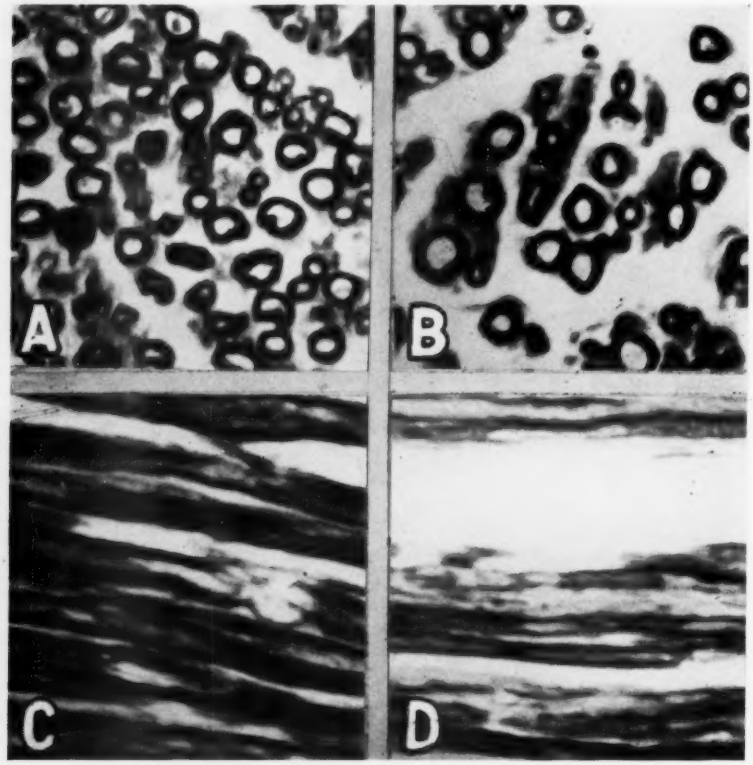

FIG. 6.—Photomicrographs (× 525). Ninety-three days after cooling.
A. and C. Cross and longitudinal sections of normal nerve stained with osmic acid. B. and D. Same of cooled nerve. This animal did not exhibit any demonstrable edema or obvious paralysis of the limb at any time, but degeneration of the nerve, as evidenced by disappearance of the myelin sheaths, is quite definite.

Few experimental studies of the effects of prolonged cooling have been reported. Smith, *et al.*,[6] in 1915, studied "trench foot" by exposing rabbits' feet to cold, damp mud, and observed subacute inflammatory changes in the involved tissues, more particularly affecting the walls of the blood vessels. Results more similar to our own were obtained recently by Blackwood and Russell,[7] who immersed rats' tails in cold sea water for 48 to 96 hours and found that degeneration of both nerve and muscle fibers followed exposure. Clinical studies of sailors whose extremities have been exposed to cold and wet for prolonged periods reveal that long-standing vascular and neurotrophic disturbances may occur,[8] with pain, possibly due to scar contracture about small nerves,[9] a troublesome late feature.

It is clear from our studies that nerves are more susceptible to damage by cooling than are other structures, so that the extensive degenerative changes in other tissues seen clinically after long exposure to cold may in part be secondary to nerve damage. It is of interest to note that the loss of all types of nerve fibers is in keeping with the clinical evidence of hypofunction of the somatic motor and sensory nerves and of the autonomic fibers to blood vessels and sweat glands. The trophic changes in the tissues resulting from a loss of their innervating fibers, also, may play a part in the prolonged delay of wound healing known to occur in such tissues,[2] and further serve as a warning against the indiscriminate use of refrigeration as a therapeutic measure when the aim is other than amputation of the refrigerated part.

SUMMARY

Immersion of a dog's limb in water at 6° C. for 96 hours results in edema and in temporary depression of sensory and motor function of the exposed extremity. It is followed by varying degrees of degeneration of the nerves in the cooled area, without demonstrable histologic changes occurring in other tissues. Although direct injury from the cold may play a minor rôle, the degenerative changes are regarded as being due essentially to ischemia of the part during and following the cooling period.

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HYPERINSULINISM TREATED BY SUBTOTAL PANCREATECTOMY

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SINCE HARRIS'[7] DESCRIPTION of the syndrome resulting from excessive secretion of insulin in 1924, many of the problems of this disease have been solved. The criteria for a diagnosis of islet cell adenoma and the indication for operation have been well stressed by Whipple.[11] The importance of considering all of the many causes of spontaneous hypoglycemia, and aids in the diagnosis of these, have been pointed out by Wilder,[12] Brunschwig,[2] and others. The use of a low carbohydrate diet for the diagnosis and management of some of these patients, as advocated by Waters,[10] has been a valuable contribution. The metabolic studies to determine the amount of carbohydrate, protein, and fat oxidized by these patients, as proposed by Conn,[4] have been an important addition to the study of the problem, and they are particularly useful in the study of questionable cases.

It has become apparent that functional hypoglycemia is a fairly common condition, while organic hyperinsulinism is quite rare. This fact makes the careful study of these patients, using every diagnostic aid available, in order to establish an etiologic diagnosis of the hypoglycemia, of the utmost importance.

When the "Whipple triad" of symptoms is present, surgical exploration of the pancreas is clearly indicated, and an islet tumor will be present in nearly all cases. This triad includes nervous system disorders, such as confusion, coma, convulsions, collapse coming on in the fasting state while the blood sugar level is 50 mg. per 100 cc., or less, and the relief of symptoms by the administration of glucose. When the blood sugar does not fall to 50 mg. per 100 cc. during an attack, a careful search for causes other than islet adenoma must be made, and the etiologic factor may be found to be one of the following conditions (Table I).

When the blood sugar, during an attack, is above 50 mg. per 100 cc. a diet low in carbohydrate, 50 Gm., or less, and high in protein will often give relief from attacks, because while 50 per cent of the protein may yield dextrose, this conversion takes place at a slow, even rate, and this fact, as well as the slower absorption rate of protein, prevents any marked elevation of the blood sugar, which would, in turn, stimulate the pancreas.

It has been shown by Conn[3] that the glucose tolerance curve is influenced by the antecedent diet in normal people as well as those with hypoglycemia. We feel that a glucose tolerance test taken after a proper preparatory diet is of definite diagnostic value in cases of hypoglycemia. Organic and functional hyperinsulinism, both, characteristically, give a low

TABLE 1

ETILOGIC CLASSIFICATION OF SPONTANEOUS HYPOGLYCEMIA (CONN)

I. Organic—recognizable anatomic lesion:
  (a) Hyperinsulinism:
    1. Pancreatic island cell carcinoma
    2. Pancreatic islet cell adenoma
    3. Generalized hypertrophy and hyperplasia of islands of Langerhans
  (b) Hepatic disease:
    1. Ascending infections—cholangitis
    2. Toxic hepatitis
    3. Diffuse carcinomatosis
    4. Fatty degeneration or metamorphosis
    5. Glycogenosis (von Gierke's disease)
  (c) Pituitary hypofunction (anterior lobe):
    1. Destructive lesions (chromophilic tumors, cysts, *etc.*)
    2. Atrophy and degeneration (Simmonds' disease)
    3. Thyroid hypofunction—secondary to pituitary hypofunction
  (d) Adrenal hypofunction (cortex):
    Atrophy or destruction of cortex
  (e) Central nervous system lesions (some interfere with nervous control of blood sugar
II. Functional—no recognized anatomic lesion:
  (a) Hyperinsulinism (autonomic nervous system imbalance)
  (b) Renal glycosuria
  (c) Pregnancy and lactation

dextrose tolerance curve, and the organic cases usually have an abnormally low fasting level. Studies on the utilization of the injected glucose are especially indicated in borderline cases. The method which we have used is that suggested by Johnston,[9] of taking a basal metabolic rate prior to injection of glucose, and repeating the metabolism test at 0.5 hour, 1 hour, 2.5 hours, and 3 hours after the injection. Urine samples are examined for nitrogen and sugar if the proportion of carbohydrate, fat, and protein utilized are to be determined. The calculation from these studies of the respiratory quotient gives diagnostic information, and is also of benefit in following the patients postoperatively.

We feel that in patients who do not conform exactly to the "Whipple triad" and yet have the symptoms of hyperinsulinism, that these studies may aid in determining the advisability of performing a subtotal pancreatectomy. Two cases which had this operation are presented, one of which had extensive pre- and postoperative studies.

CASE REPORTS

Case 1.—M. B., white, female, age 19, single, was first seen April 11, 1935. Her chief complaints were severe headaches and abdominal cramps. She also had a chronic cough, and had excessive weight gain. Roentgenograms of the chest and skull were both negative. Her basal metabolism rate was minus five. At this time the patient was taking one grain of thyroid daily. Fasting blood sugars were 78 and 99 mg. per cent.

In January, 1936, the patient admitted having had frequent attacks of weakness, sweating, tremor, and a metal reaction described as stuporous. This was associated

with the lack of food, and was quickly relieved by the ingestion of carbohydrate. At this time a glucose tolerance test was made and the results are shown in Chart 1. Blood sugar levels taken during attacks were from 55–60 mg. The family history was essentially negative, except for the occurrence of diabetes in an aunt on the maternal side. The patient's past history was noncontributory.

Physical Examination.—The patient appeared to be a well-developed, slightly obese female, in no apparent distress. She was 5 feet, 5¾ inches in height, and 165 pounds in weight (estimated normal weight 138 pounds). Except for obesity and midepigastric

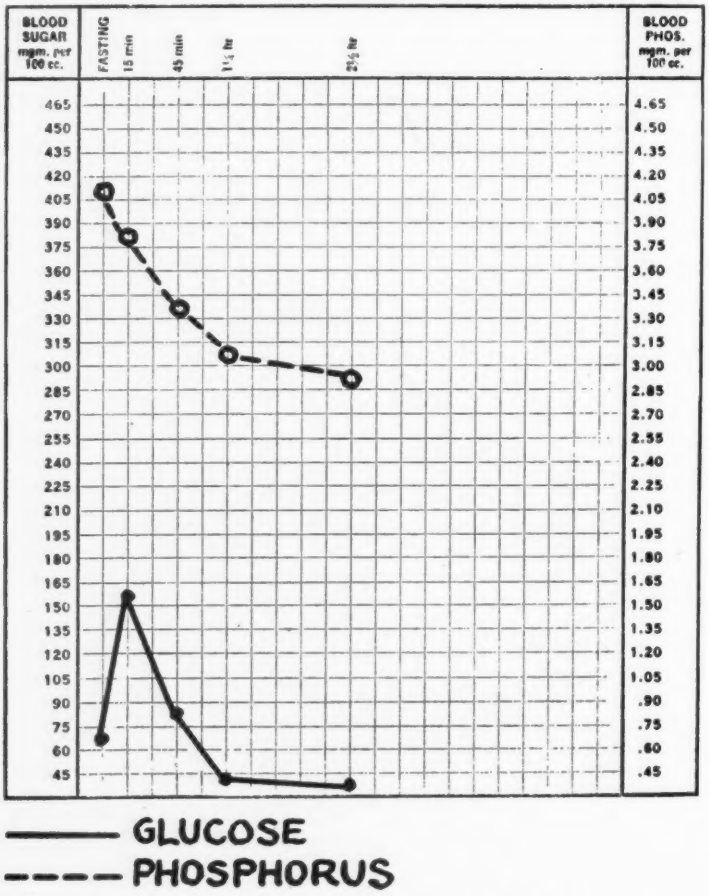

CHART 1.—Case 1: Preoperative glucose tolerance and phosphorus curves.

tenderness on palpation the physical examination was normal. The chest was clear, the heart normal, blood pressure 118/74. Routine laboratory examinations, including uranalysis and blood count, were negative. *Clinical Diagnosis:* Spontaneous hypoglycemia.

Operation.—February 10, 1936: No tumor was found and, so, approximately two-thirds of the pancreas was removed. During the operation the patient was given 400 cc. of glucose intravenously and 500 cc. of whole blood. Hourly, postoperative blood sugar determinations were made and measured 250, 230, 230, 170, and 140 mg. per cent, respectively.

Daily, fasting blood sugar determinations were made postoperatively and measured 135, 129, 111, 129, 105, 104, 75, 93, 96, 84, and 89, respectively. The postoperative

course was uneventful. The patient remained asymptomatic. The microscopic appearance of the gland was described as normal. Two months afterwards, a glucose tolerance was made and the results are shown in Chart 2.

The patient made an uneventful recovery. She has had no return of symptoms and blood sugar tests taken each year have remained normal. The pre- and postoperative respiratory quotients are shown in Chart 3.

Case 2.—M. C., white, female, age 43, married, first entered the hospital, August 25, 1942, with complaints of nervousness, backache, low blood pressure, and sinus trouble.

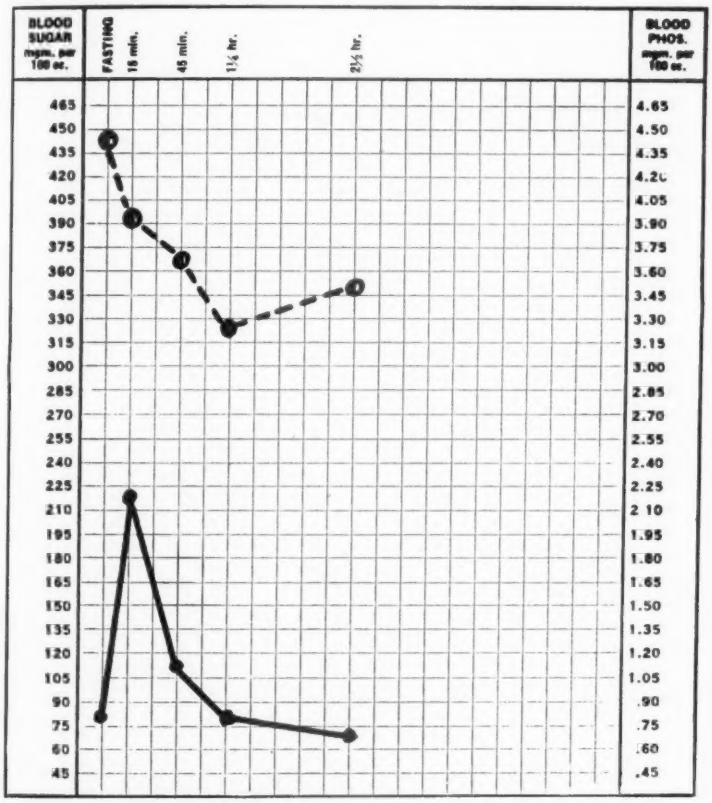

CHART 2.—Case 1: Postoperative glucose tolerance and phosphorus curves.

Her first attacks of nervousness began in 1929, and were characterized by weakness, nervous irritability, excessive perspiration, and ravenous hunger, all occurring about three hours after meals, being worse after exercise, and which were relieved by eating, especially readily available carbohydrate. From her own experience she learned to eat four or five meals daily, yet lost weight gradually. Her attacks became progressively more severe, and soon began to occur in the early morning, and as early as one hour after meals. Further symptomatology included memory loss during attacks, mental cloudiness, speech difficulty, and visual disturbances. There was never any loss of consciousness. Personality changes made their appearance because of the patient's symptoms occurring when out with other people.

The patient's past history was essentially noncontributory, and consisted, in the main, of a number of unsuccessful operations designed to alleviate her symptomatology. The family history was of interest in that exactly similar symptoms were found in members of three successive generations—the father, one brother, and a daughter.

Physical examination was essentially normal. The patient was a well-developed and well-nourished white female, measuring 5 feet, 2 inches in height, and weighing

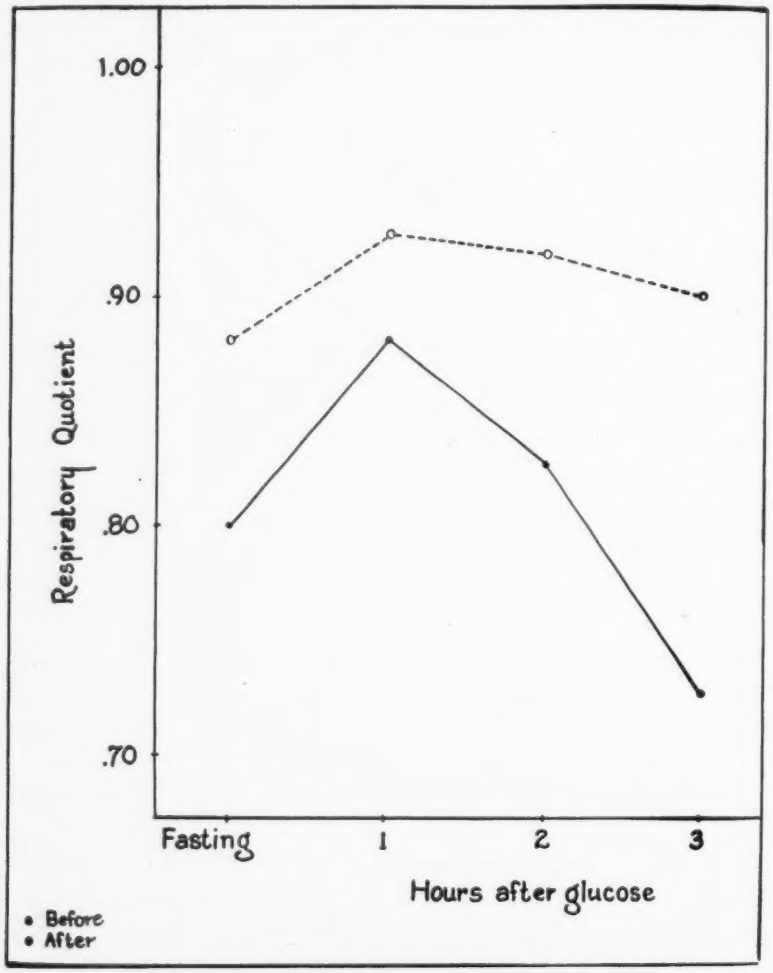

CHART 3.—Case 1: Respiratory quotient before and after operation.

119 pounds. The head and neck were normal. The chest was resonant, breath sounds normal. The heart was not enlarged, the rhythm regular, heart sounds normal, no murmurs heard. Blood pressure 95/60. Except for well healed postoperative scars, the abdomen presented no abnormalities. No masses were palpable. Examination of the extremities and pelvis was likewise normal.

Laboratory Data.—The Kline exclusion test for syphilis was negative. The blood count was normal—hemoglobin 14.9 Gm., R. B. C. 4,870,000; W. B. C. 7,600, with 51 per cent polys. Urinalysis was negative, and the stool examination normal. Fasting blood sugars varied from 61 to 69 mg. per cent. Other special examinations were also

made. Blood diastase measured 13.0. Cephalin-cholesterol liver function test was one plus. In the serial 2 mg.-bromsulfalein test there was no retention of dye in 20 minutes. The B. M. R. was minus five, R. Q. 0.77. Twenty-four-hour urine for quantitative sugar was negative. Fractional gastric analysis was normal; and except for poor "B" bile, transduodenal biliary drainage was negative. Roentgenograms of the spine, skull, chest, gallbladder, stomach and duodenum were all normal. Severe

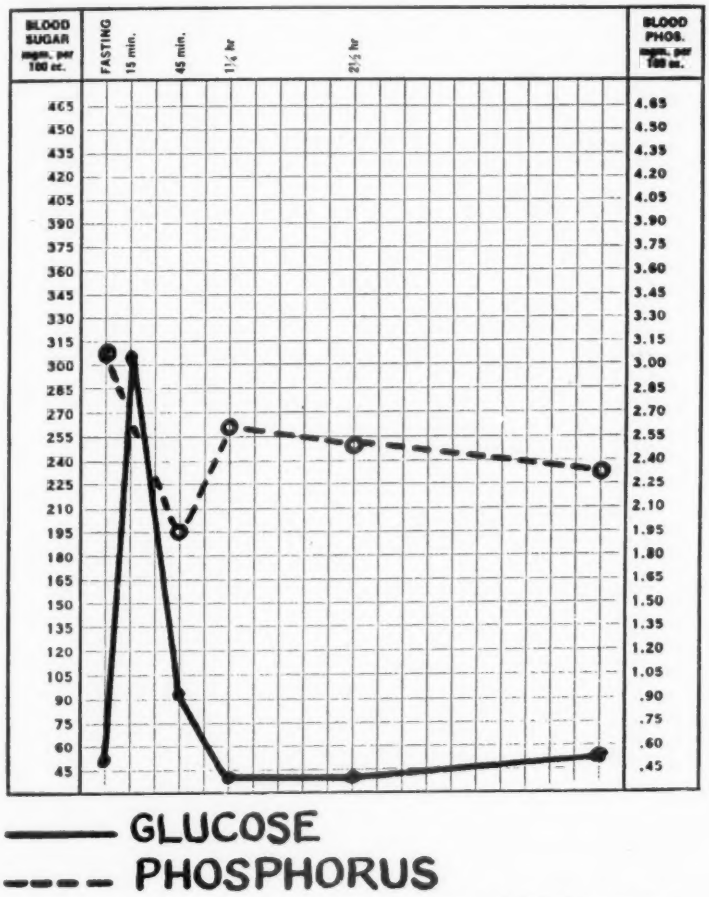

CHART 4.—Case 2: Preoperative glucose tolerance and phosphorus curves.

symptoms were induced in the fasting state by strenuous exertion, at which time the blood sugar measured 60 mg. per cent. One milligram of epinephrine was given subcutaneously, with relief of all symptoms within 15 minutes, when another blood sugar specimen measured 73 mg. per cent.

The patient was discharged, September 2, 1942, on a high protein, low carbohydrate diet, with 5–6 meals daily, and thyroid extract grain 0.5 daily. Despite this program, symptoms became gradually more severe, and the patient was readmitted January 24, 1943, and, again, on April 11, 1943. Glucose tolerance tests were repeated on each of these occasions, and the last one had to be terminated at the end of 1.75 hours because of the severity of the hypoglycemic reaction (Chart 4). On this latter occasion further laboratory observations were made. The blood N. P. M. measured 26.5 mg. per cent,

blood sodium 332, blood potassium 17.5. The B. M. R. was now plus four, the R. Q. 0.80. The cephalin-cholesterol test was plus three, and the intravenous hippuric acid test measured 0.98 Gm. Prothrombin was 100 per cent.

The patient was transferred to the Surgical Service for operation, April 22, 1943. In preparation for operation she was given 500 cc. of 10 per cent glucose intravenously. This was followed in 1.5 hours by a reaction which required the injection of 50 cc. of 50 per cent glucose for relief. During the operation she was given 500 cc. of 10 per cent glucose and 500 cc. of whole blood. The tail of the pancreas was found to be hyperplastic and firm, but no adenoma could be found, and approximately five-sixths

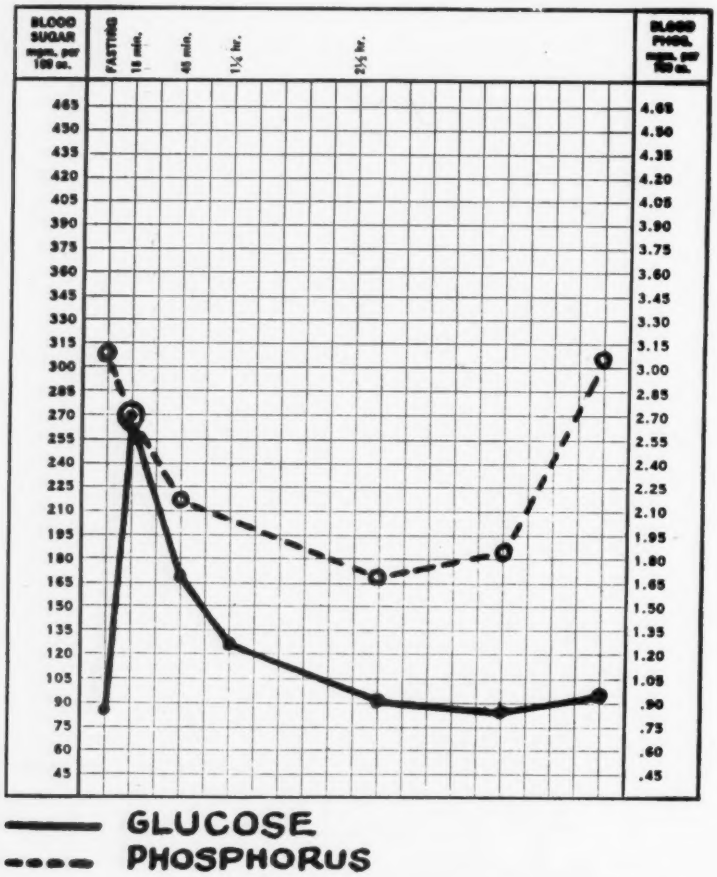

CHART 5.—Case 2: Postoperative glucose tolerance and phosphorus curves.

of the gland was resected. The microscopic examination of the gland was described as normal. Postoperative blood sugar determinations were made hourly, and measured 108, 91, 85, 109, 127, 131, 145, 112, 132, 98 respectively. A glucose tolerance test was made 24 hours postoperatively, and the results are shown in Chart 5. Daily blood sugars varied between 80 and 100 mg. per cent. Postoperatively, the serum cholesterol level was 135 mg. per cent and the total plasma fat 450. Analysis of stool specimens for fatty acids, neutral fat, and total fat, after the ingestion of a high fat meal, was within normal limits, showing satisfactory function with regard to the pancreatic external secretions.

The patient's postoperative course was completely uneventful. She is at present enjoying excellent health and has had no return of symptoms. The fasting blood sugar level has been between 80–100 mg. per cent since the operation.

DISCUSSION.—The failure to find an islet adenoma in these cases was at first disappointing, but the excellent results obtained following subtotal pancreatectomy has led us to agree with David[5] and Womack,[13] that this is the procedure of choice when no adenoma can be found, after a careful search of the pancreas and the usual sites where heterotopic pancreatic tissue sometimes occurs.[8] While excellent results may be expected following a subtotal resection, we would again like to caution against anything less than a subtotal resection. The function which the pancreas plays in digestion was found not to be affected significantly when four-fifths of the gland had been removed.

The use of a high protein, low carbohydrate diet for a preoperative trial is excellent. We have, in some cases, experienced difficulty in getting patients to refrain from the ingestion of some carbohydrate when the prodromal symptoms of an attack appear. The symptoms are quite unpleasant, and the patients' complete confidence is necessary to keep them from escaping this by taking a little carbohydrate, which they have found relieves them, at least temporarily.

Hyperplasia of the islet cells is difficult to be sure of pathologically, just as it is difficult to tell which tumors are benign and which are malignant. This difficulty has previously been expressed by Womack,[13] and also by Frantz.[6] The microscopic appearance of the two cases here reported was described as normal.

SUMMARY

Two additional cases presenting the syndrome of spontaneous hypoglycemia, and in which no islet tumor could be found, are reported. The very satisfactory results obtained following subtotal resection in these cases makes us confident that no actual islet tumor existed. Emphasis is again directed to the fact that a large amount of pancreas must be resected in these cases.

The study of metabolism of glucose in these patients after they have been on a standard preparatory diet may be of benefit in a diagnostic way and in evaluating the results of treatment.

The removal of a large amount of the pancreas does not seem to cause any subsequent digestive or metabolic disturbance.

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STELLATE GANGLION BLOCK

A NEW ANTERIOR APPROACH

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THE TEMPORARY INTERRUPTION of sympathetic impulses by the injection of procaine hydrochloride about the sympathetic ganglia is a recommended therapeutic procedure in acute vascular injuries.[1, 2, 3, 4, 5, 6, 7, 8] The purpose of the injection is to overcome secondary spasm of the collateral vessels. Reflexes, arising in the damaged segment of a blood vessel and transmitted by the sympathetic nervous system, give rise to this spasm. In time of war, with the great increase in the number of patients suffering from vascular injuries of the extremities, a simple technic for the injection of the sympathetic ganglia is desirable. This is especially true when one recognizes that the majority of these cases will, of necessity, be cared for by physicians whose experience in this field of surgery is more or less limited. The technic for injecting the lumbar sympathetics is not difficult. The prominent landmarks and the absence of important structures in the immediate vicinity of this portion of the sympathetic chain make this procedure relatively simple. This is not true of the sympathetic supply to the upper extremity which is generally interrupted by infiltration in the region of the stellate ganglion. This structure lies close to the great vessels of the neck (Fig. 1), and is intimately related to the dome of the pleura. Recently, a soldier was admitted to this hospital suffering from ischemia of the upper extremity secondary to trauma of the brachial artery. Repeated attempts by various members of the surgical staff to interrupt the sympathetic supply to this extremity were unsuccessful. The purpose of this report is to present a technic for stellate ganglion block, which was developed as a result of this experience, and which has proven successful in our hands.

Two approaches to the stellate ganglion have been generally employed. One technic employs a posterior paravertebral route and is essentially the method described by Labat,[9] in 1924. The "occasional" operator finds it difficult to advance the tip of the needle forward along the vertebral body sufficiently to contact the sympathetic chain and at the same time avoid the pleural cavity. The parietal pleura is in intimate contact with the thoracic vertebrae, and the advancing needle must pass between them. With the second method the stellate ganglion is injected by inserting the needle anteriorly just above the clavicle.[10, 11] In the latter technic failure to interrupt the sympathetic pathway has been frequent. The tip of the needle often enters one of the great vessels of the neck and on changing the direction sufficiently to avoid these structures contact with the vertebra cannot be made. In addition, with the cutaneous puncture site just above the

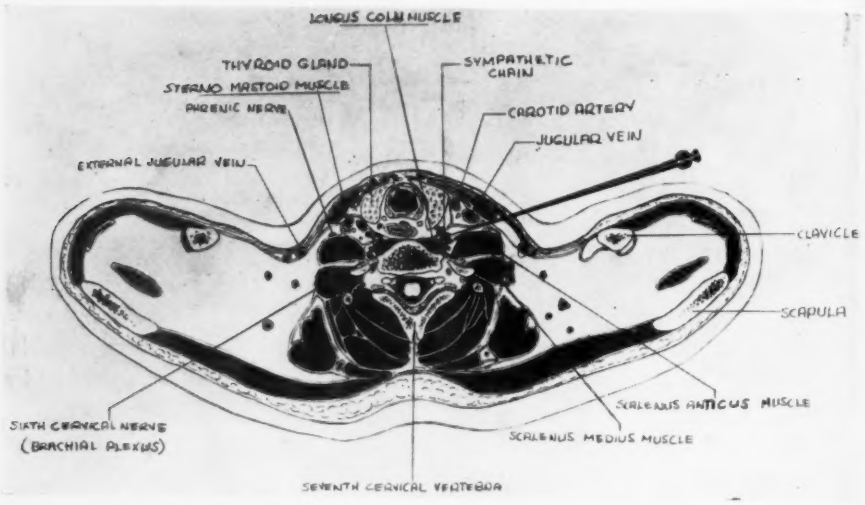

FIG. 1.—Anatomic drawing of a cross-section of the neck at the level of the cricoid cartilage with the needle directed posteriorly and medially at an angle of 15 degrees with the ventral surface of the scalenus anticus muscle.

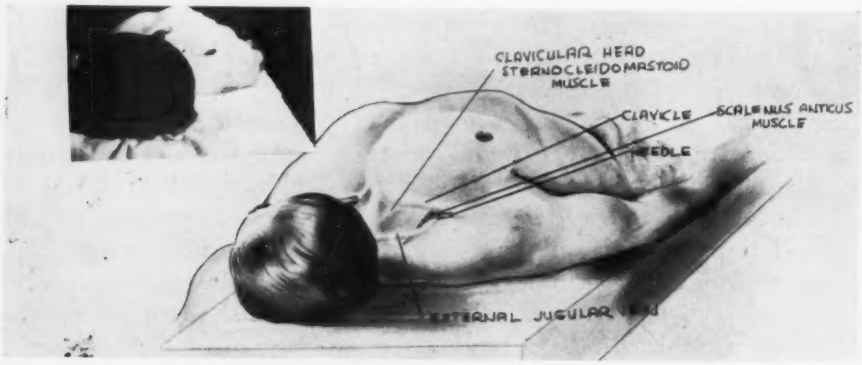

FIG. 2.—Sketch of patient with needle in place illustrating its relationship to the important landmarks. Inset, photograph of the same patient.

Technic of Stellate Ganglion Block by the Proposed Anterior Approach. The patient is placed in a supine position on a firm bed. The skin is surgically prepared and the landmarks, *i.e.*, the cricoid cartilage and scalenus anticus muscle, are identified by palpation. The latter is more easily felt if the patient's face is turned toward the opposite side and the neck extended. A thin pillow under the patient's shoulders gives adequate extension of the neck. The external jugular vein crosses the lateral edge of the scalenus anticus muscle at the level of the puncture site (cricoid cartilage), and is an aid to its identification. A wheal of novocaine is made at the point of puncture, *i.e.*, at the edge of the scalenus anticus muscle, and in the same place as the cricoid cartilage. A fine lumbar puncture needle is introduced through this wheal and directed posteriorly and medially in line with the cricoid cartilage at a 5 to 15 degree angle with the horiontal plane (bed). The point of the needle contacts the anterolateral surface of the 7th cervical vertebra at a depth of 3.5 to 6 cm. If contact with the vertebra is not made, the needle should be withdrawn and reinserted with the tip directed more posteriorly. The needle is withdrawn from immediate contact with the vertebra to clear the point of the periosteum prior to injection. Before the novocaine solution is introduced, the needle should be aspirated to ascertain that it does not lie within a blood vessel or the subarachnoid space. It is possible to enter the latter through one of the vertebral foramens. Ten cubic centimeters of a 2% novocaine solution are then injected. There is sufficient spread of the solution through the fascial planes to block completely the sympathetic supply to the upper extremity. Evidence that the solution has been properly placed is the development of a Horner's syndrome, *i.e.*, ptosis of the upper lid, slight elevation of the lower lid with narrowing of the palpebral fissure, enopthalmos, contracted pupil and anhidrosis. In addition to the above changes there is a marked congestion of the conjunctiva due to dilatation of its vessels. This phenomenon usually occurs within ten minutes after the injection.

clavicle the cervical projection of the apex of the lung is frequently injured, resulting in the development of pneumothorax. Although this complication usually is not followed by serious sequelae, it should be avoided.

The stellate ganglion, formed by the fusion of the inferior cervical and first dorsal sympathetic ganglia, lies on the anterolateral surface of the first thoracic and 7th cervical vertebrae between the head of the first rib and the vertebral artery. Frequently it exhibits a length of 2.5 cm. The cervical sympathetic trunk immediately above the ganglion lies on the deep fascia of the neck covering the anterior surface of the longus capitis and longus colli muscles (Fig. 1). This fascia is continuous with, and in the same plane as, the deep fascia covering the anterior surface of the anterior scalene muscle. The phrenic nerve which lies on the deep fascia covering the anterior scalene muscle, therefore, lies lateral to, but in the same plane as, the cervical sympathetic trunk. The internal jugular vein, carotid artery, and vagus nerve, enclosed in their fascial sheath, lie anterior to these muscles. The dome of the pleura and apex of the lung extend well above the clavicle anteriorly and to the lower edge of the first rib posteriorly. Dissections of the neck performed upon cadavers have confirmed the above anatomic relations. With the patient supine, it was found that if an ordinary spinal puncture needle was inserted at the level of, and directed toward, the cricoid cartilage, it would pass above the apex of the lung. If this puncture site was at the lateral edge of the scalenus anticus muscle and the needle was inserted with the point directed posteriorly so that the shaft made an angle of from 5 to 15 degrees with the horizontal plane, the needle would pass behind the great vessels and contact the body of the 7th cervical vertebra (Figs. 1 and 3). Frequently the point of the needle was found in contact with the stellate ganglion.

Clinical application of this approach was successful in 67 out of 70 attempts (95.7 per cent). Furthermore, these injections have been carried out by four different medical officers, which is supporting evidence in favor of the accuracy and simplicity of the procedure.

Complications arising as a result of the injection of the stellate ganglion by this approach have been few. The patients almost universally complain of pain when the deep fascia near the vertebral column is pierced, but this discomfort is only transitory. The novocaine solution, in addition to surrounding the sympathetic chain, has occasionally spread to the spinal nerves resulting in temporary hypoesthesia and paresis of the corresponding upper extremity. The seventh and eighth cervical and first thoracic roots are the ones usually involved. Fluoroscopic examination of our patients, following the injection, have failed to reveal diaphragmatic paralysis as a result of spread of the solution to the phrenic nerve. With the phrenic nerve and cervical sympathetic trunk lying in the same fascial plane such diffusion could easily occur. The needle entered the subarachnoid space in one case as shown by aspiration of spinal fluid. It should be noted that the needle passed through the intervertebral foramen without causing pain. The

needle was withdrawn, replaced, and the stellate ganglion injected. No untoward symptoms were noted on this patient. Although procaine is a relatively nontoxic drug, the danger of a toxic reaction must be constantly borne in mind. This danger can be minimized, according to Weiss,[12] by

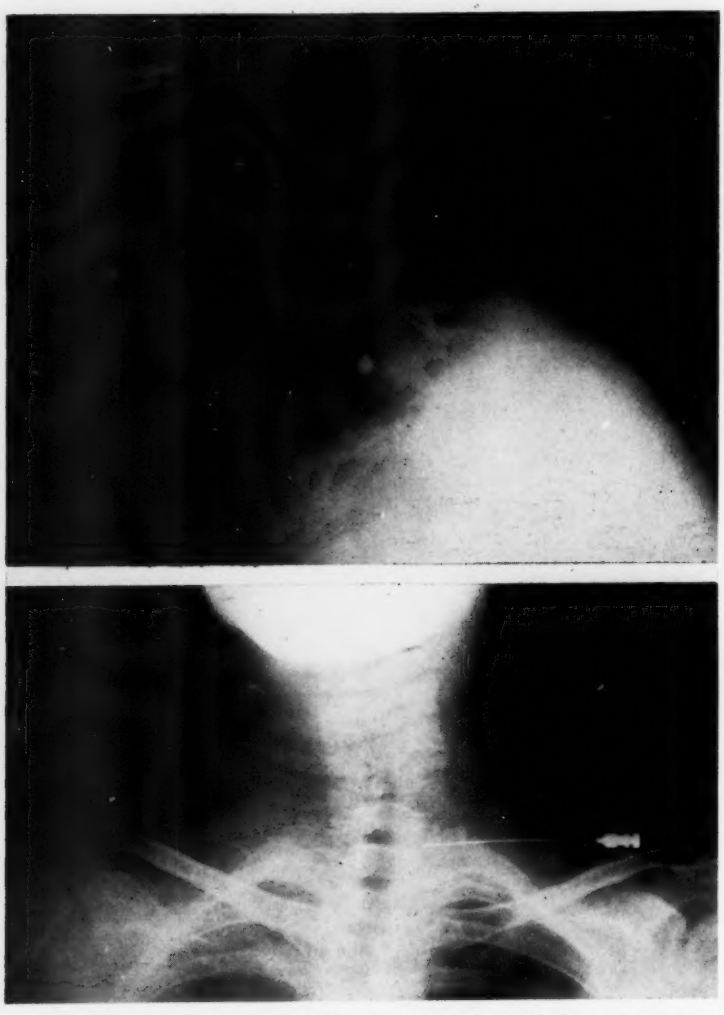

FIG. 3.—Lateral and anteroposterior x-rays of a patient with the needle in place. The tip of the needle can be seen to be in the anatomical location of the stellate ganglion, *i.e.*, at the inferior border of the body of the 7th cervical vertebra. The needle is also seen to be above the apical portion of the lung.

the preliminary use of one of the barbiturates. This has been done in all of our cases and no evidence of procaine reaction has been noted.

SUMMARY

1. An anterior approach for injection of the stellate ganglion has been described.

2. The complications encountered with this method have been briefly discussed.

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CONGENITAL ATRESIA OF THE ESOPHAGUS: WITH TRACHEO-ESOPHAGEAL FISTULA

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DURING THE LAST THREE YEARS seven infants with congenital atresia of the esophagus were admitted to the Vanderbilt University Hospital. A tracheo-esophageal fistula, Vogt's type $3B^1$ was present in each case. All of these patients were operated upon. The operative procedures have varied, but in all cases the fistula has been exposed at operation. An end-to-end anastomosis of the segments was attempted in three cases and it was possible to bring the ends of the segments together in two of them. One patient survived and is living. This child is six months old.

A summary of the cases is presented in Table I, and the one case in which a successful anastomosis was effected is reported in detail.

Case Report.—R. L. C., male, born November 28, 1943, in the Vanderbilt University Hospital, at term. He was the first child of a healthy and normal mother, age 33. At birth the infant weighed 6 lbs., 7.75 ounces. He breathed spontaneously, and physical examination revealed no abnormalities. Thirty-six hours after birth it was noted that the child had an unusually large amount of mucous in his mouth and throat, and 56 hours after birth the following note was made by the Pediatric intern: "Baby having a large amount of mucous and is vomiting practically all fluids offered. Believe this baby should be investigated for possibility of tracheo-esophageal fistula." The infant was given 50 cc. of blood plasma and 50 cc. of 10 per cent glucose intravenously and 200 cc. of normal saline solution subcutaneously, and a catheter was passed into the pharynx. The tube could be inserted for a distance of only six inches, where it met an obstruction. The infant was then taken to the Roentgenologic Department, where a swallow of radiopaque oil revealed the esophagus to end in a blind pouch about two inches below its origin. The presence of large amounts of gas in the gastro-intestinal tract confirmed the diagnosis of congenital atresia of the esophagus, with tracheo-esophageal fistula.

The patient was transferred to the Surgical Service. At this time his weight was 5 lbs. 12.5 ounces. The breath sounds were rough throughout both lung fields but there was no evidence of consolidation. The patient showed no evidence of dehydration.

He was given 25 cc. of blood plasma and 25 cc. of 10 per cent glucose solution intravenously, and 100 cc. of normal saline subcutaneously, and taken to the operating room 84 hours after birth.

Operation.—The skin of the posterior neck and back was prepared with soap, sterile water and alcohol. The skin and subcutaneous tissues about the line of incision were infiltrated with 0.5 per cent procaine solution. No other anesthesia was used throughout the procedure.

An incision about six centimeters long was made about one centimeter to the left of the spinus processes, extending between the spine and the border of the scapula. The 3rd, 4th, and 5th ribs were divided and segments of the ribs about one centimeter in length were excised. The ribs were retracted forward. The intercostal muscles were divided and the parietal pleura was carefully stripped from the surface of the transverse processes and the spine. This dissection was carried down until the mediastinum

The author wishes to express his appreciation to Dr. Mary Clark of the Department of Pediatrics, for her untiring efforts in the postoperative care of this patient.

TABLE I

SUMMARY OF CASES

Case No. and Admission Date	Age (Days) at Operation	Time (Hours) of Delay in Operation Following Diagnosis	Operative Procedure	Anesthetic	Duration of Life After Operation	Remarks
1. 9-25-41	4	24	Rt. 6th intercostal space, transpleural approach. Lower segment ligated at fistula, divided and brought out to skin of left posterior chest wall. Cervical esophagostomy.	Ether vapor. (Positive pressure).	Expired on operating table during closure of wound.	Lower segment very small at its upper end. Fistula posterior surface of trachea just above carina. *Autopsy:* Early bilateral bronchopneumonia.
2. 10-22-41	5	24	10-23-41: Rt. paravertebral, retropleural approach. Lower segment exteriorized as above. Small opening made through pleura during operation. 10-25-41: Cervical esophagostomy.	Drop ether (open mask)	10 days.	Lower segment very small at its upper end. Fistula at the carina. Imperforate anus and rectovaginal fistula also present. Autopsy not performed.
3. 9-4-42	8	36	Rt. paravertebral retropleural approach. Lower segment visualized. Patient stopped breathing and condition so poor ligation was not accomplished. Wound closed. Gastrostomy performed.	Drop ether (open mask)	3.5 hours.	Lower segment fairly well developed. Fistula high posterior wall of trachea. Upper segment long. *Autopsy:* Bilateral bronchopneumonia. Abscess left upper lobe.
4. 4-16-43	6	6	4-16-43: Fistula not exposed at first operation. Cervical esophagostomy. Ligation of esophagus at hiatus through abdominal approach. Gastrostomy. 5-11-43: Lt. 8th intercostal space, transpleural approach. Lower segment esophagus excised, after ligation fistula. Diaphragm incised and stump of esophagus turned into stomach.	4-16-43 Drop ether (open mask). 5-11-43 Ether vapor and oxygen. (Positive pressure).	28 days after 1st operation. 3 days after 2nd operation.	Lower segment very small at its upper end. Fistula posterior trachea, just above the carina. *Autopsy:* Gastropleural fistula. Empyema.
5. 9-20-43	7	24	High Rt. paravertebral, retropleural approach. Fistula ligated. Attempted end-to-end anastomosis. Sutures pulled out. Wound closed. Cervical esophagostomy. Abdomen opened. Lower segment esophagus divided at hiatus. Lower stump turned into stomach. Gastrostomy.	0.5% novocaine	12 hours.	Upper end of lower segment small and delicate. Fistula posterior aspect of trachea almost in the carina. Autopsy not performed.
6. 11-28-43	3	12	Reported in detail. Left posterior retropleural approach.	0.5% novocaine.	Living.	
7. 1-27-44	2	24	High right paravertebral approach. Fistula ligated. End-to-end anastomosis over No. 14 F. catheter. Same procedure as described for Case 6. Extreme tension on suture line posteriorly. Wound closed without drainage.	0.5% novocaine.	30 hours.	Upper segment very short. Upper end lower segment small. Fistula posterior, 5 mm. above carina. *Autopsy:* Empyema, right, mediastinitis. Segments separated posteriorly.

was reached. Three upper intercostal arteries were divided between clamps and were ligated with fine silk. In this way the arch and upper portion of the descending aorta could be mobilized and retracted forward. After a rather lengthy search, the upper blind pouch of the esophagus was located and its lower portion was freed. A traction suture of silk was placed through the lower end of this pouch. The trachea was then exposed. The right and left main stem bronchi were identified and the lower segment of the esophagus was found attached to the carina (Fig. 1). It was freed and a ligature of fine silk was placed around the lower end of the esophagus close to the carina. A. No. 10 F. catheter was placed through the infant's nose into the upper segment of the esophagus. A very small opening was then made through the lower end of the

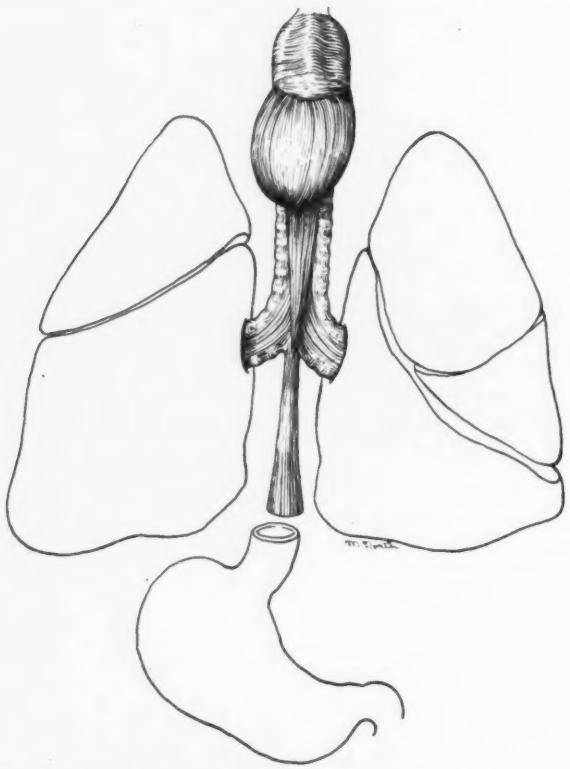
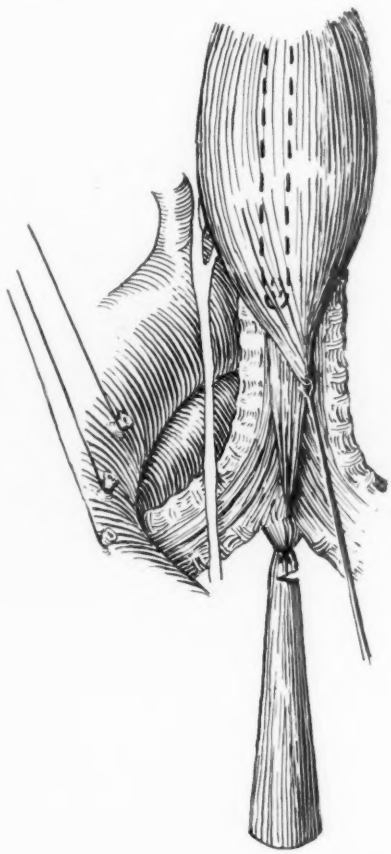


FIG. 1.—Sketch showing the deformity observed in Case 6. (Posterior view)

blind pouch of the esophagus.. The catheter was passed through this opening into the wound. The exposed portion of the lower segment of the esophagus was of extremely small caliber and had a very thin wall. With the scissors a small nick was made in the side of the wall of the lower segment about five millimeters below the silk ligature (Fig. 2). The end of the catheter was then threaded through this opening into the lumen of the esophagus and passed downward for a distance of about six inches. Another ligature of fine silk was then placed around the esophagus and was tied tightly over the lower segment of the esophagus and the enclosed rubber catheter about three millimeters below the opening through which the catheter was placed (Fig. 3). The lower segment of the esophagus was then divided completely between the two ligatures. Slight upward traction was placed on the catheter. In this way the lower

segment could be pulled upward a little way. Interrupted fine silk sutures were placed in the wall of the upper segment and through the wall of the lower segment below the ligature so that when these sutures were tied the lower segment was inbricated into the upper segment (Fig. 4). Interrupted fine silk sutures were placed in this manner around the entire circumference of the esophagus. Toward the end of this procedure a small hole was inadvertently made in the parietal pleura, so that a pneumothorax was created.



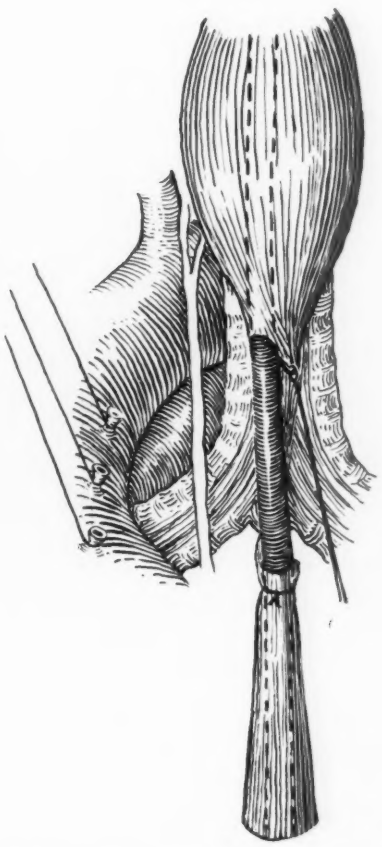


FIG. 2.—The upper intercostal arteries have been divided between ligatures and the arch of the aorta displaced. A traction suture fixes the end of the upper pouch, into which has been passed a small catheter. The lower segment has been ligated just below the fistula and an opening has been made through the side of the wall of the lower segment.

FIG. 3.—The catheter has been passed through a small opening at the lower end of the upper pouch and through the opening in the wall of the lower segment, downward into the stomach. The lower segment has not yet been completely divided.

A small rubber tissue wick was placed into the wound and its end was left about one centimeter lateral to the esophagus. The surface of the wound was dusted with two grams of sulfanilamide powder. The soft tissues of the wound were brought together and sutured in layers with interrupted fine silk sutures. Traction on the catheter was maintained while closure of the wound was effected. A Logan's bow was applied to the child's face and the catheter was strapped to the bow with adhesive in such a way as to maintain the traction which had been applied to the catheter.

The child was given oxygen throughout the procedure. There were short periods of cyanosis but at the end of the procedure the child's general appearance was fairly good.

Postoperative Course.—Immediately upon return to the ward, the patient was placed in a warm incubator crib in the Trendelenburg position. Oxygen was given by means of a mask placed near the face. Twenty cubic centimeters of blood plasma and 20 cc. of 10 per cent glucose solution were administered intravenously, and 60 cc. of normal saline were given subcutaneously. Fluids were administered in this manner every four hours during the next two days.

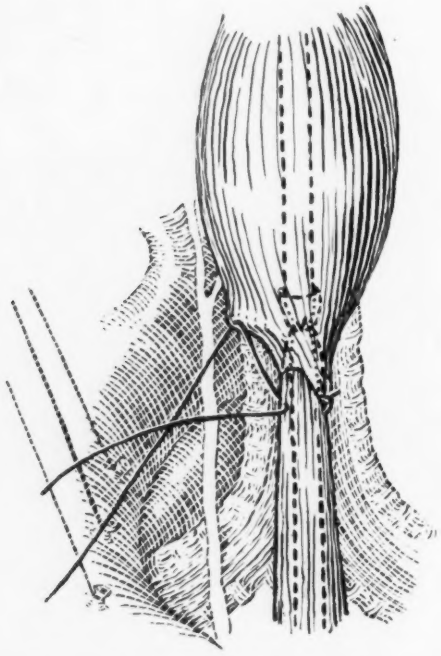


FIG. 4.—The long segment has been completely divided and is being imbricated into the upper segment. Considerable traction has been placed on the catheter to pull the lower segment upward slightly.

Forty-eight hours after the operation it was noted that there was no tension on the catheter, and that it could be moved up and down through the esophagus.

Feedings of 10 per cent glucose every two hours were begun, through the catheter, 48 hours after operation. Two days later he was begun on 15 cc. of skimmed milk formula every two hours.

Occasional episodes of cyanosis followed the accumulation of mucous in the mouth and throat. Scattered moist râles were heard over both lung fields, and a roentgenogram of the chest, made seven days after operation, showed some scattered, hazy areas of decreased penetration throughout both lung bases.

On the seventh postoperative day the esophageal catheter became obstructed, and despite repeated attempts it could not be reopened. It was thought to be inadvisable to remove the catheter because of the belief that a stricture at the site of anastomosis was almost certain to occur. Gastrostomy was performed and small feedings of formula and 10 per cent glucose solution were begun 24 hours after operation. Feedings were

gradually increased in amount until the normal calculated quantity of formula was given, in 12 daily feedings, ten days following gastrostomy.

During this period of time the esophageal catheter was left in place. Two weeks after gastrostomy was performed an attempt was made to deliver the end of the catheter through the gastrostomy wound. The tube could not be found, even by direct vision through a small esophagascope inserted through the gastrostomy wound. Repeated attempts were made to find the catheter during the succeeding ten days, when this was accomplished by means of a simple hooked probe. A braided silk string was tied to the end of the catheter, the catheter removed through the nose and the string left through the esophagus.

Dilatations were begun with a No. 12 F. retrograde bougie the following day, five weeks after the original operation. Five days later a No. 16 F. bougie was passed with little resistance. The child then suddenly developed a severe diarrhea. Innoculation of the corneae of a rabbit revealed a virus, recently described by Buddingh and Dodd[2] as the cause of severe stomatitis and diarrhea in infants. Cultures from the mouth of the intern caring for the patient revealed the presence of the virus and indicated the source of the infection.

Dilatations were not carried out then for ten days. During this time the patient's diarrhea had become very severe. In spite of the frequent administration of blood plasma the patient became edematous. When regular dilatations were begun again, a No. 14 F. bougie was passed with some difficulty.

After two weeks the diarrhea subsided completely. Since then the child has gained weight progressively. Dilatations have been continued once or twice weekly; and at the present time the patient weighs 18 pounds. He appears to be developing normally and is taking all of his feedings by mouth. A No. 30 F. bougie is being passed through the esophagus at intervals of one week. Roentgenologic examination reveals a narrowing at the site of the anastomosis, but there is no delay of thin barium feedings at the site of the stricture.

Discussion of Cases.—In attempting to evaluate the cases which have been operated upon, several factors are apparent. In the first case observed, a tight-fitting mask and positive pressure anesthesia were employed. During the course of the operative procedure the stomach became greatly distended with gas. It should be realized that this is bound to occur, since the stomach communicates with the trachea. The same thing occurred at the time of the second operation upon Case 4. In this case the esophagus had been ligated with umbilical tape at the esophageal hiatus of the diaphragm through an abdominal incision. Twenty-five days afterward the infant coughed up a small amount of the feeding which had been given through the gastrostomy tube. At operation, and later at autopsy, it was proven that the esophagus had recanalized. The tape ligature was found lying within the lumen of the cardiac end of the stomach at autopsy.

Thus, a transpleural incision is not desirable if one expects to resort to the use of the tightly-fitting mask and positive pressure anesthesia. Furthermore, simple ligation of the lower segment of the esophagus, particularly at its lower end, is likely to be followed by recanalization of the esophagus two or three weeks later.

A posterior retropleural incision was employed in five of these cases. In four of these the incision was made on the right side, the azygos vein being

doubly ligated and divided. We feel that this is preferable to an incision on the left side, where the arch of the aorta lies in the way. The one successful operation reported here was accomplished through an incision made on the left side, however.

The position of the fistula between the lower segment and the trachea is variable. In two of the cases reported here the fistula was directly at the carina. In the remaining cases the fistula was in the posterior wall of the trachea, somewhat above the bifurcation. The length of the upper segment varies also. In Case 7, the upper segment was unusually short, and tension on the suture line was extreme. Exteriorization of the upper segment and gastrostomy should have been resorted to in this case when it became apparent that the anastomosis could not be satisfactorily accomplished. The distance between the two segments in Case 6 was all of two centimeters. The upper segment was fairly long and although the fistula was at the carina and the upper end of the lower segment was extremely small, it was possible to "telescope" it into the upper segment because of the mobility of the upper segment and the slight upward displacement of the lower segment which was effected by means of traction on the catheter.

In Case 5 the operative procedure was too great. Cervical esophagostomy and gastrostomy should have been deferred and performed at another time.

COMMENT: There have been approximately 400 cases of this type of congenital abnormality reported. The condition is undoubtedly more common than this number would seem to indicate.

There have been two methods of approach to the surgical treatment of this condition. The first aims to interrupt the continuity of the lower segment of the esophagus and to create an esophagostomy by bringing the upper segment to the skin of the neck. The construction of a subcutaneous epithelial-lined tube to communicate between the upper segment of the esophagus and the stomach is undertaken later. Such a plan obviously requires several operations. The second plan is directed toward the establishment of continuity of the esophagus within the thorax. The latter plan, accomplished in a single operation, is the ideal one.

Leven,[3] in 1941, reported the first successful operation for congenital esophageal atresia, with tracheo-esophageal fistula. This child was operated upon in November, 1939, and is still alive. A gastrostomy was first performed, followed at successive operations by extrapleural ligation of the fistula and cervical esophagostomy. An external esophagus has since been constructed. Since that time several additional successful procedures of this type have been reported (Ladd, Humphreys, Haight).

In June, 1943, Haight and Towsley[4] reported the first successful operation for the establishment of the continuity of the esophagus. Since then, seven additional successful operations have been reported, five by Haight,[5] one by Humphreys,[6] and one by Ladd.[7]

It is our belief that the fistula should be exposed at operation in all cases and that it should be closed and the lower segment of the esophagus divided

as near the fistula as possible. In the seven cases reported here, the fistula has been exposed at the first operation upon six patients, and ligation and division of the lower segment was performed in five.

Following closure of the fistula an attempt should be made to effect an anastomosis of the two segments of the esophagus. The upper segment lies very high in the thorax, and its length is variable in different infants. It may be exposed by dissecting just behind the trachea. It is usually easily recognizable. Its position is not fixed, as is the end of the lower segment, but it moves up and down with movements of the child.

If the distance between the two segments is so great, or the lower segment is so delicate, that a direct anastomosis cannot be accomplished, the wound may be closed and the infant turned on his back, where a short incision may be made along the anterior border of the lower end of the left sternocleidomastoid muscle. The upper segment can be easily located, freed, and brought out to the skin. It should be pointed out that the operation performed upon the one successful case in this series was upon an infant in whom the lower segment communicated with the trachea at the carina and that the upper end of the lower segment was very poorly developed, being composed on its anterior side of only the mucous membrane. A procedure such as the one employed here may be useful in the construction of an intrathoracic esophagus even when there is a considerable defect in the continuity of the esophagus and where the lower segment is so poorly developed as to make end-to-end suture, without the aid of a catheter, or some similar device, impossible.

Thus, by directly attacking the fistula, one may accomplish end-to-end suture in a fair number of patients, and if it is obvious at operation that this cannot be done, the upper segment may still be exteriorized. Gastrostomy should then be performed. If the infant's condition is poor, the last two procedures should be deferred until later.

SUMMARY

Seven infants have been operated upon in the Vanderbilt University Hospital for congenital atresia of the esophagus during the last three years. The author's experience in the management of these patients is reviewed. In one case a successful end-to-end anastomosis of the esophageal segments was performed. This child is living, and is in good condition. This case is reviewed in detail.

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VARICOSE VEINS

Anatomic Findings and an Operative Procedure Based Upon Them

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The published results of the therapy of varicose veins and post-thrombophlebitic processes in the thigh and leg still leave much to be desired. Though high ligation offers many advantages over older methods of treatment, too often (as pointed out by Harkins,[1] Ochsner and Mahorner,[2] and others), the desired improvement is not achieved because other sites in the lower limb possess incompetent or potentially incompetent perforator veins not controlled by the operative procedure. Our own study of 214 patients who had had high ligation combined with retrograde injections of sclerosing solution showed that, in 46 per cent, the result was not wholly satisfactory (Table I), some even requiring further operative procedures.

Table I

Results* in 214 patients (372 lower limbs) treated by high ligation and retrograde injection of sclerosing solution

	No.	Per Cent
Faulty high ligations	19	5
Improvement — Objective		
Reflux flow of blood 16–40 seconds†	201	54
Reflux flow of blood 0–15 seconds†	171	46
Improvement — Subjective		
75–100%†	189	51
50– 75%†	82	22
Less than 50%†	101	27

* Average length of time since operation 3 years, 8 months.

† Multiple tourniquet tests were employed and observations taken with the tourniquet applied at the groin in order to rule out inaccuracy of the high ligation procedure.

Of the various tests designed to locate the incompetent perforator veins, contributing to the poor results mentioned, probably the most important is the multiple tourniquet test. This yields valuable information but is not sufficiently precise to disclose the exact location of the incompetent perforator veins.

The evident failure of therapy in a considerable number of cases and the inadequacy of the tests for the location of incompetent perforator veins in the thigh led to anatomic studies on the cadaver. In a preliminary report[3] the results of dissections on 19 cadavers (36 thighs), and 43 surgical dissections were outlined. Since that time, anatomic dissections have been carried out on 54 additional cadavers (101 thighs) and 703 surgical dissections have been made. These not only have confirmed the studies previously reported but have yielded additional anatomic data which form the basis of a surgical procedure giving promise of materially improving the therapy of varicose veins by aiding in the elimination of incompetent or potentially incompetent perforator veins of the thigh.

It is the purpose of this paper to present the results of these anatomic studies and describe the operative procedure to which they contributed.

ANATOMIC STUDIES

The location and number of perforator veins connecting the saphenous system with the deep veins of the thigh vary greatly. Nevertheless, certain generalizations can be made. For instance, the long saphenous vein consistently joins the femoral vein in the inguinal region. Despite many variations, the superficial epigastric, superficial iliac and superficial pudendal veins are always represented in some manner. Dissections of the thigh disclosed the fact that, although variations are numerous, there is a scheme of placement of the long saphenous vein and the perforator veins of the thigh, so that there may be said to be a general pattern (Fig. 1, Type I) with three main variations in type (Types II, III and IV) described below.

The embryonic pattern of the saphenous system (Type I, Fig. 1) consists of two saphenous stems in the thigh. The main long saphenous vein (B) is usually larger, deeper and more medial than the accessory vein (A). In the upper part of the thigh both tributaries of the long saphenous vein (A, B) are found in the expected location, superficial to the deep fascia. At a varying level (C) in the upper half of the thigh, however, one tributary (B′) of the main long saphenous vein B pierces the superficial layer of the deep fascia, thereafter coursing deep to the deep fascia, whereas the accessory saphenous vein A remains superficial to the deep fascia throughout its entire course. This tributary (B′) which courses beneath the superficial layer of the deep fascia, assumes great importance because from it arise the main perforator tributaries which connect it with the femoral and popliteal veins of the thigh (Fig. 1, H, J, K), discussed later. After coursing down the thigh for six centimeters, or more, this deep saphenous tributary again divides. One tributary (B‴) emerges from beneath the deep fascial layer at D to reoccupy a position superficial to the deep fascia and the other (B″) continues down the thigh and leg between deep fascial layers.

Type II (Fig. 2) varies from Type I in the absence of the accessory saphenous vein A. Type III (Fig. 3) varies from Type I in that the accessory saphenous vein A, although present, does not connect with the femoral vein near the saphenous-femoral junction, but does connect with the main saphenous vein at C just above the site where the main saphenous vein dips beneath the deep fascia. Type IV (Fig. 4) is like Type I except for an apparent lack of connection at C between the lower end of the accessory saphenous vein A and the main saphenous vein B. The saphenous vein, or any of its divisions or tributaries, may be double or even triple, and considerable variation may exist in the manner in which the perforator tributaries of vein B′ connect with the deep circulation.

MID-HUNTER CANAL PERFORATOR VEIN

Along with the observations made on the saphenous vein and its subdivisions, described above, it was noted first in anatomic then in surgical

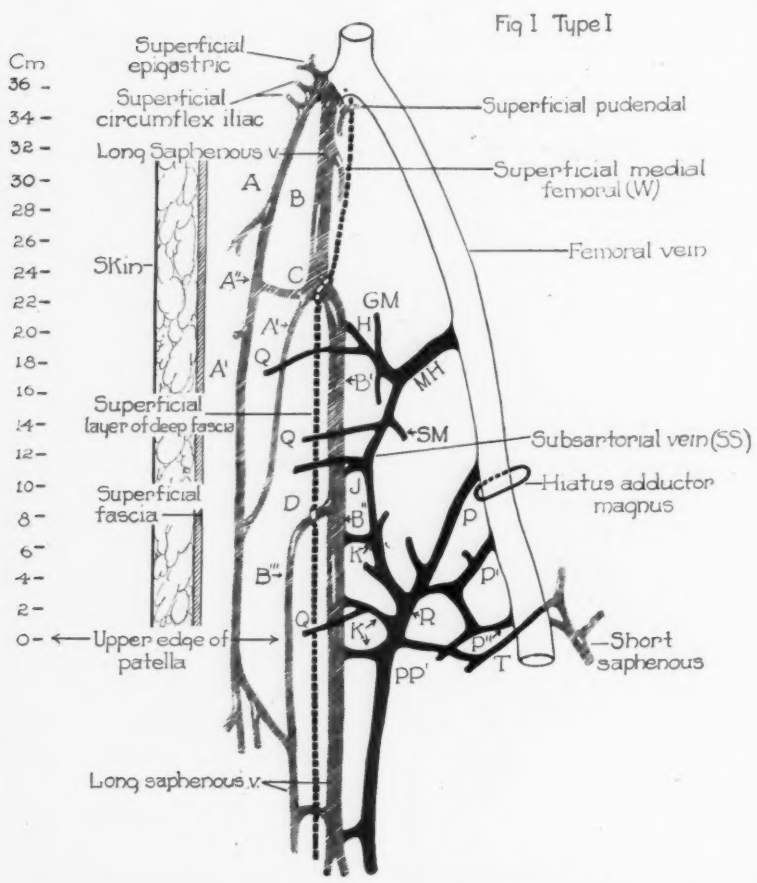

FIG. 1.—Drawing showing the saphenous system as A, A′, A″, and B, B′, B″, B‴. Veins A, A′, A″, B lie superficial to the deep fascia, whereas distal to C, veins B′, B″ lie beneath the superficial layer of the deep fascia. Vein B‴ emerges from beneath the deep fascia at D.

Perforator vein H connects the main saphenous vein B′ with the constant mid-Hunter canal perforator vein MH.

The genicular venous plexus is composed of the highest genicular vein, P, superior medial genicular vein, P′, inferior medial genicular vein, P″, and a tributary, T, of the short saphenous vein. A tributary, PP′, of the deep saphenous drains the medial aspect of the leg and empties into the genicular plexus.

The subsartorial vein connects the mid-Hunter canal vein with the genicular plexus at R.

Accessory perforator veins, Q, emerge into the superficial fascia without making direct connections with the main saphenous stem B′ B″. Perforator veins J, K make direct connections between the main saphenous stem B″ and the subsartorial vein.

SM and GM are tributaries draining the sartorius and gracilis muscles.

dissections, that at a point in the thigh varying from 16 to 22 cm. above the upper edge of the patella, lies a constant tributary (MH) of the femoral vein. This tributary, accompanied by a branch of the femoral artery and one of the saphenous nerve, pierces the deeper fascial layers to become more superficial than the femoral vein. It divides into several tributaries which drain adjacent muscles, especially the gracilis (GM) and sartorius (SM). Of utmost importance is the fact that, with great constancty, *at least one of these tributaries of vein MH connects with the deep saphenous vein* (*B′*) in the midthigh. Because this perforator vein (MH, H, Fig. 2) connects

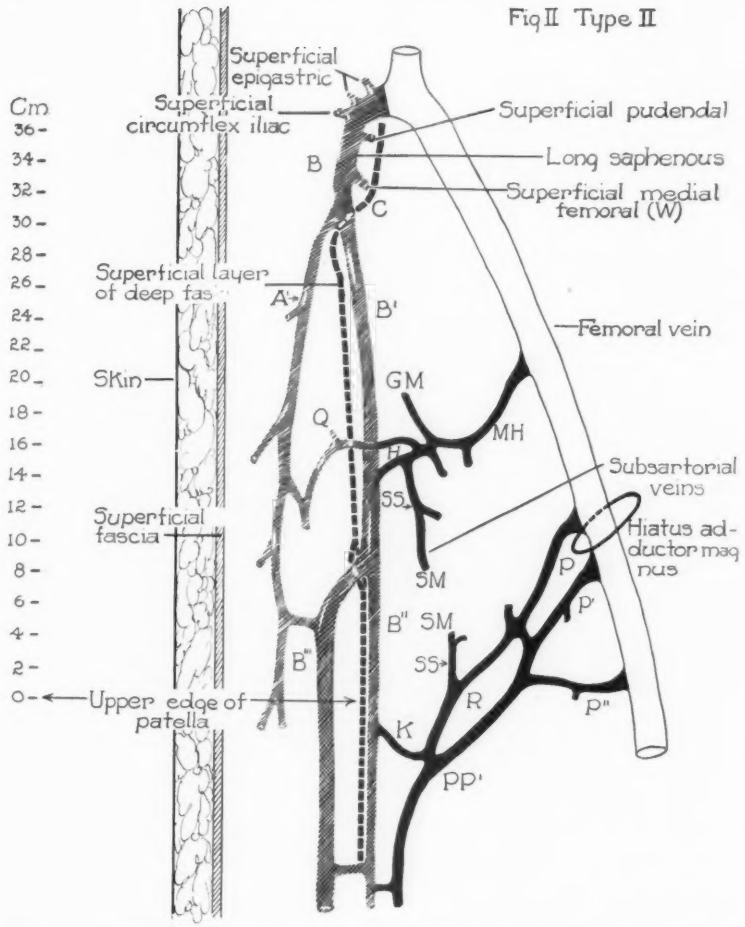

FIG. 2.—Drawing showing the saphenous system as B, B′, B″, B‴, A′. (Note that the saphenous system in the upper thigh consists of a single stem, B). Veins B, A′, B‴ lie superficial to the deep fascia, whereas distal to C, Veins B′, B″ lie beneath the superficial layer of the deep fascia.

Perforator vein H connects the main saphenous vein B′ with the constant mid-Hunter canal perforator vein MH.

The geneicular venous plexus is composed of the highest genicular vein, P, superior medial genicular P′, inferior medial genicular vein P″. A tributary, PP′, of the deep saphenous drains the medial aspect of the leg and empties into the genicular plexus.

The subsartorial vein (SS) consists of a proximal segment which drains into the mid-Hunter canal plexus and a distal segment which drains into the genicular plexus at R.

Accessory perforator vein Q emerges into the superficial fascia without making direct connection with the main saphenous stem B′. Perforator vein K makes direct connection between the main saphenous stem B″ and the genicular plexus.

SM and GM are tributaries draining the sartorius and gracilis muscles.

with the femoral vein at about the middle of Hunter's canal it has been designated as the mid-Hunter canal perforator vein. In a total of 56 consecutive anatomic examinations, this vein was found in each.

Another constant tributary of the mid-Hunter canal vein (MH) is one that drains the sartorius muscle. This tributary (SS) has been given the name of subsartorial vein. After coursing distally for a few centimeters, it most often terminates within the sartorius muscle (Fig. 2) but in a con-

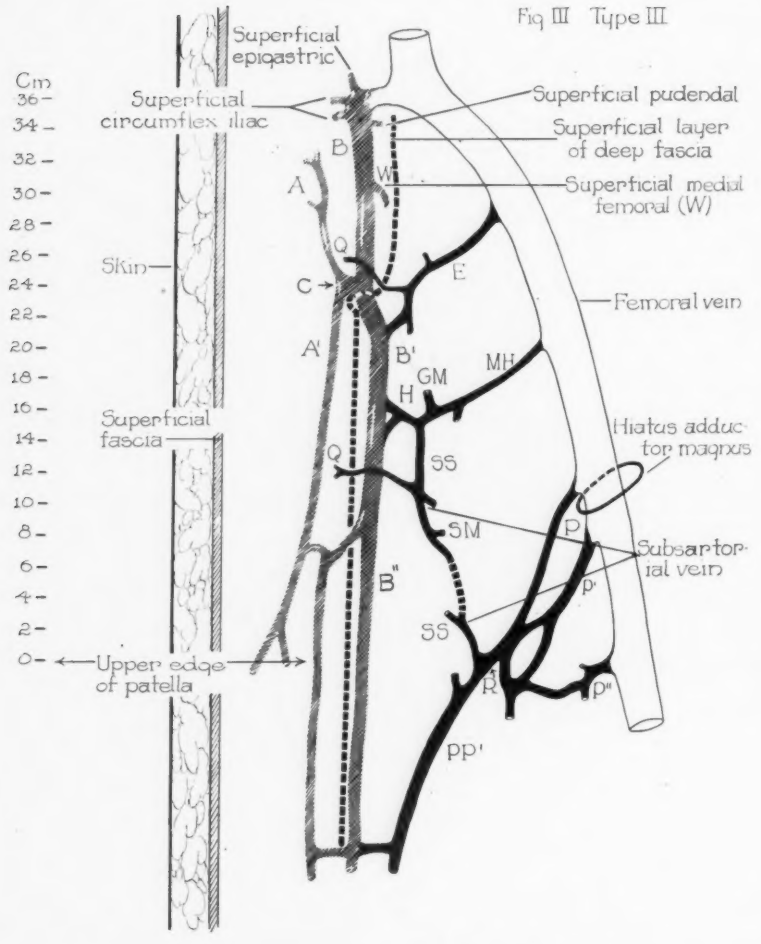

FIG. 3.—Drawing showing the saphenous system as A, A′, B, B′, B″. Note that vein A connects with the main saphenous stem B at point C but makes no apparent connection with the proximal end of vein B. Veins A, A′, B lie superficial to the deep fascia, whereas distal to C, veins B′, B″ lie beneath the superficial layer of the deep fascia.

A high-Hunter canal perforator vein, E, occasionally connects the proximal portion of vein B′ with the femoral vein. Perforator vein H connects the main saphenous vein B′ with the constant mid-Hunter canal perforator vein MH.

The genicular venous plexus is composed of the highest genicular vein, P, superior medial genicular vein, P′, inferior medial genicular vein, P″. A tributary, PP′, of the deep saphenous drains the medial aspect of the leg and empties into the genicular plexus.

The subsartorial vein SS makes connections within the sartorius muscle between the mid-Hunter canal vein and the genicular plexus at R. Accessory perforator veins, Q, emerge into the superficial fascia without making direct connections with the main saphenous stem B′.

SM and GM are tributaries draining the sartorius and gracilis muscles.

siderable number of cadavers it was found not only to drain this muscle but to continue distally to connect with the vein PP′ at R (Fig. 1). The importance of this subsartorial vein lies in the fact that from it often arise perforator tributaries which connect with the deep saphenous vein B′ or B″. It is interesting to note that, whenever the upper subsartorial vein ends within the sartorius muscle, a tributary of the vein PP′, arising at R, travels

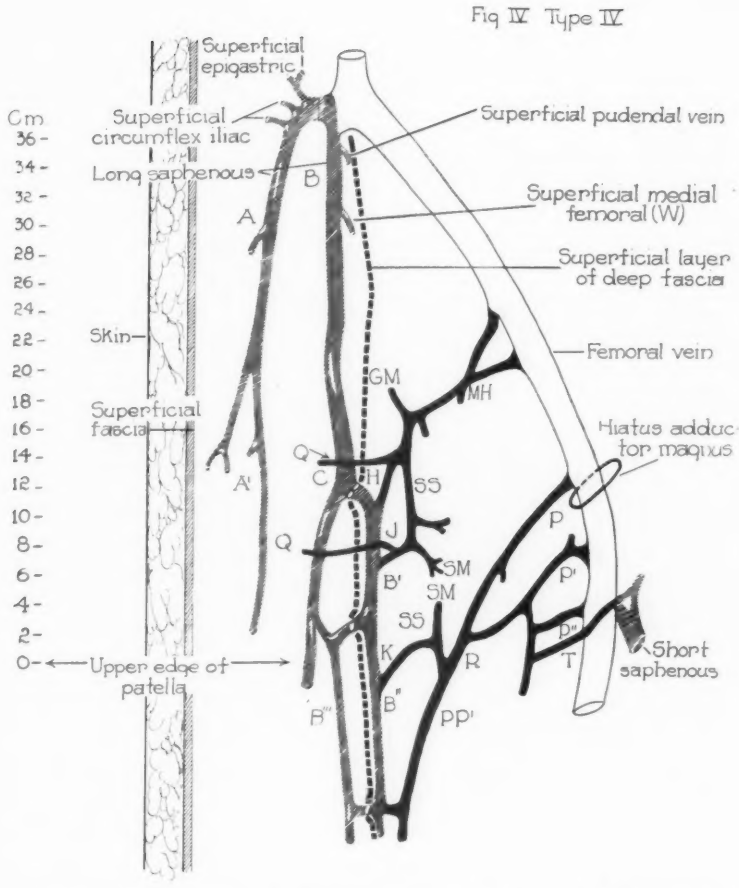

FIG. 4.—Drawing showing the saphenous system as A, A', B, B', B''', Note that vein A, A' makes no apparent connection with vein B at C. Veins A, A', B lie superficial to the deep fascia, whereas distal to C, veins B', B'' lie beneath the superficial layer of the deep fascia.

Perforator vein H connects the main saphenous vein B' with the constant mid-Hunter canal perforator vein MH.

The genicular venous plexus is composed of the highest genicular vein, P, superior medial genicular vein P', inferior medial genicular vein P'' and a tributary, T, of the short saphenous vein.. A tributary, PP', of the deep saphenous drains the medial aspect of the leg and empties into the genicular plexus.

The subsartorial vein, SS, consists of a proximal segment which drains into the mid-Hunter canal venous plexus and a distal segment which drains into the genicular plexus at R.

Accessory perforator veins, Q, emerge into the superficial fascia without making direct connections with the main saphenous stem B'. Perforator veins J, K make direct connections with the main saphenous stem B'B'' and the subsartorial vein SS.

SM and GM are tributaries draining the sartorius and gracilis muscles.

proximally to enter the sartorius muscle (Figs. 2 and 4) and sometimes connects with the upper subsartorial vein within the sartorius muscle (Fig. 3). Again, even though the lower subsartorial vein apparently has no direct connection with the upper subsartorial vein, it also may possess perforator tributaries (K) which connect with sapheous vein B'' (Fig. 4).

In four cadavers and twelve surgical dissections a relatively rare tributary (E, Fig. 3) was found. This particular vein, aside from furnishing

tributaries to adjacent muscles, connects the upper part of the deep saphenous vein B′ with the femoral vein at a point from six to eight centimeters below the sapheno-femoral junction. This vein may possibly be a constant tributary of the femoral vein, but because connections between it and the saphenous vein B′ are rare, no detailed studies have as yet been attempted. In future dissections, however, this vein will be investigated more thoroughly.

GENICULAR VEIN PLEXUS

The area superficial and deep to the deep fascia of the upper and medial aspects of the leg is drained by a tributary PP′ of the saphenous vein. This tributary extends proximally beneath the insertion of the sartorius muscle, passes between the sartorius and gracilis muscles, and lies beneath the deep fascial layer at the lower level of the knee . It anastomoses with the inferior (P″) and superior (P′) medial genicular veins below the hiatus of the adductor magnus muscle. Also, it often possesses a connection with a triubtary (T, Fig. 4) of the short saphenous vein. This saphenous tributary (PP′) then courses upward to become the highest genicular vein (P) which pierces the aponeurotic covering of the adductor canal and connects with the femoral vein immediately above the hiatus of the adductor magnus muscle. The saphenous nerve accompanies this saphenous tributary of the highest genicular vein. The importance of the saphenous tributary PP′ lies in the fact that veins often connect it with the deeper saphenous vein B″ by tributaries (K). Moreover, as previously mentioned, this vein PP′ occasionally connects with the subsartorial vein at R (Fig. 1). Of utmost importance is the fact that from the tributary veins MH, H, SS, J and K often arise one or more tributaries which extend independently into the superficial tissues, having no connection with the main saphenous vein. These veins (Q, Fig. 4) have been designated as accessory perforator veins.

Figures 1, 2, 3 and 4 are composite illustrations abstracted from studies on the cadaver and are designed to indicate the most important variations in the placement of the veins of the medial portion of the thigh.

It is to be noted that the constant veins B′, B″, H, MH, SS, PP′, P and P′ are present in all four types. Also the inconstant veins, J, K, E and Q may be present in any of these types. Again, although in all types the vein B usually pierces the superficial layer of the deep fascia at about the junction of the upper with the middle third of the thigh, there may be some variation in this arrangement and to emphasize such variation, vein B is depicted in Figure 2 as piercing the fascia high in the thigh, while other possible sites are indicated in Figures 1, 3, and 4. The distribution of veins by type in the cadaver and in surgical dissections is shown in Table II. Table III shows measurements taken from dissections on the cadaver.

Figures 1 to 4 show main groups of perforator veins on the medial aspect of the thigh: namely those of (a) the sapheno-femoral junction; (b) the mid-Hunter canal vein; and (c) the genicular plexus. In the literature upon this subject, it has been stated that there are from one to seven perforator

TABLE II

CLASSIFICATION ACCORDING TO TYPES OF VEINS IN THIGH

	Dissections‡			
	Anatomic		Surgical	
	No.	Per Cent	No.	Per Cent
Type I	9	8.91	43	7.5
Type II	62	61.38	365	64.0
Type III	3	2.97	14	2.5
Type IV	27	26.74	149	26.0
Total typed	101		571†	

* A total of 137 anatomic and 703 surgical dissections (465 patients) formed the series, of which 101 and 571, respectively, were typed.

† The cases before 1942 were not classified, as a sufficiently definite pattern had not been established.

TABLE III

MEASUREMENTS‡ NOTED IN ANATOMIC DISSECTIONS

	Greatest Length Cm.	Shortest Length Cm.	Average Length Cm.	No. of Dissections
Sapheno-femoral junction	37.00	32.00	35.25	137
Point C (Fig. I)	33.00	13.50	20.37	101
Junction, mid-Hunter perforator with saphenous	20.30	11.10	15.60	67
Junction, mid-Hunter perforator with femoral	23.00	15.00	18.50	56
Junction, highest genicular with femoral	13.00	9.00	10.60	34

‡ All measurements were taken from the upper edge of the patella.

veins connecting with the long saphenous vein. In 101 anatomic dissections the largest number found was six, the smallest, one, the average number being 1.94. All these perforator veins were found to arise from the mid-Hunter canal vein, the genicular plexus or the subsartorial vein which connects them.

Further anatomic studies on the veins of the thigh demonstrated that many other perforator veins exist, but with the exception of three main sites, discussed under operative treatment, they pierce muscles, and the protection afforded by these muscles seems to preclude the possibility that these veins will become incompetent.

Six principal findings resulted from the anatomic dissections described above: (1) The recognition of a pattern in the placement of the long saphenous vein and its tributaries, with the occurrence of four anatomic types. (2) The fact that the main stem (B) of the long saphenous vein lies deep to the deep fascia somewhere along its course (B′, B″) rather than remaining superficial to the deep fascia. (3) A constant tributary (MH) of the femoral vein, named the "mid-Hunter canal perforator vein" by reason of its position, connects by one or more tributaries with the long saphenous vein as it courses beneath the deep fascia. (4) The genicular vein plexus is constant. (5) The subsartorial vein occasionally connects the mid-Hunter canal vein with the genicular system. (6) The so-called perforator veins on the medial aspect of the thigh arise mainly from the sapheno-femoral junction, the mid-Hunter canal vein, the genicular plexus, and the subsartorial vein.

SURGICAL APPLICATION

The treatment of incompetent or potentially incompetent perforator veins in the thigh depends upon a full realization of the importance of the pattern described under anatomic findings and especially of the rôles played by the deep saphenous tributary B′, the mid-Hunter canal perforator system and the genicular plexus. Eradication of the deep long saphenous stems B′ and B″ disconnects the direct communication of the saphenous vein with the femoral or popliteal veins, but does not eliminate the indirect accessory perforator (Q) veins. To efface all incompetent or potentially incompetent perforator veins of the medial thigh requires, in addition, transection of the mid-Hunter canal vein (MH) near the femoral vein, transection of the vein PP′ deep to the point R and excision of certain parts of the subsartorial vein. This should prevent the reflux flow of blood from the deep veins of the thigh by severing those incompetent veins which communicate between the deep and superficial systems.

The surgical procedure based upon the information gained from the anatomic studies described is one which, in our hands, has materially improved the results of the therapy of varicose veins. Furthermore, it involves a minimal amount of trauma and has the advantage of keeping patients in bed for very short periods of time. It consists of a combination of injection of veins, high ligation of the saphenous vein, elimination of the main saphenous stem (B′, B″), eradication of the mid-Hunter canal vein and, in certain cases, excision of the high-Hunter canal vein (Fig. 5) and elimination of as much of the genicular venous plexus as may seem to be required. The basically new approach is the employment of sclerosing solution as an agent for suppression of hemorrhage so that the surgical procedure can be performed without danger of postoperative bleeding. Patients can be out of bed and active within 24 hours after operation. The early activity combined with firm thrombosis of the cut veins also reduces the danger of pulmonary infarcts by emboli.[4]

OPERATIVE PROCEDURE

Varices below the knee are thoroughly sclerosed by local injection previous to operation. Under local or spinal analgesia, sodium pentothal or other general anesthesia, the sapheno-femoral junction is exposed through a longitudinal incision. After identification of the saphenous vein, a clamp is applied to stem B of this vein and a retrograde injection of about four cubic centimeters of a sclerosing solution is used. An interval of from 10 to 15 minutes is then allowed to elapse during which time the upper ends of the long saphenous vein or veins are dissected and their upper tributaries exposed, ligated and divided. The procedure of the high ligation[5, 6] is now so fully standardized that further comment on this aspect of the operation is unnecessary. In the majority of patients with double long saphenous veins, most of the tributaries at the upper end of the saphenous system arise from vein A. A ligation performed as indicated by M (Fig. 5) would

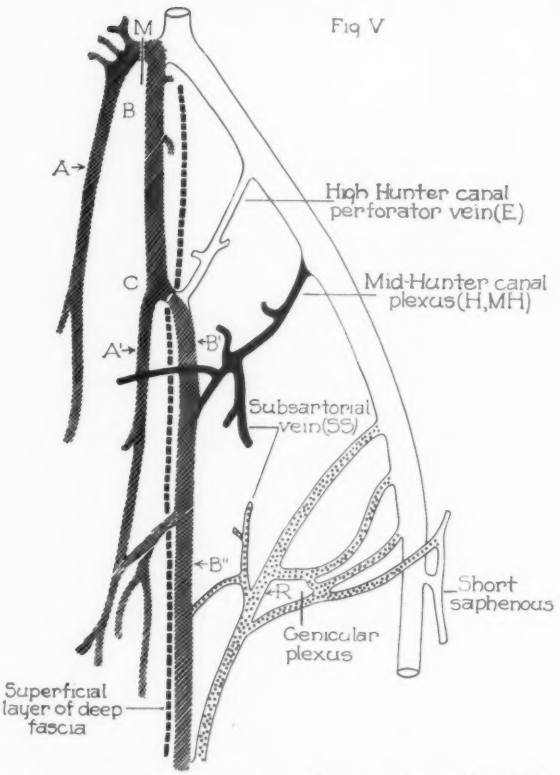

FIG. 5.—Drawing showing the saphenous system as A, A', B, B', B''. Veins A, A', B lie superficial to the deep fascia, whereas distal to C, veins B, B'' lie beneath the superficial layer of the deep fascia.

R designates the point at which the subsartorial vein connects with the genicular plexus.

Line M illustrates the danger of mistaking superficial vein A for the main saphenous vein, in patients who possess double long saphenous veins.

leave vein B patent and the operative procedure would fail to accomplish its purpose.

At the end of 10 or 15 minutes it will be found that the sclerosing solution has caused a thrombosis in the affected vessels which usually will prevent bleeding when the veins are transected. It is important, however, to test the effectiveness of the sclerosis by momentarily releasing the clamp and observing that no fresh blood flows from the open end of the vein. If bleeding should occur, as rarely it does, more sclerosing solution should be injected. If there is doubt that the sclerosing solution has effectually suppressed all hemorrhage, the tributaries of the offending vessel should be ligated, or if the bleeding cannot be exactly located, firm bandaging of the limb will control it.

The next step is the elimination of the perforator veins of the thigh. Although the point at which the main saphenous vein dips beneath the superficial layer of the deep fascia is usually located at about the junction of the upper and middle thirds of the thigh, its exact position is variable.

After transecting the nearly constant superficial medial femoral vein which lies in the superficial fascia on the inner aspect of the upper eighth of the thigh, a Mayo stripper may be placed outside the main saphenous vein and the vein stripped distally until rather marked resistance is encountered, which is usually at or about point C. When this is located, a longitudinal incision about eight centimeters in length is made over, and parallel with, the saphenous vein just distal to the point of resistance. Vein B′ is identified and tributary A′ is separated from the main saphenous vein B, B′. Once the vein B′ is identified it is simple to ascertain that it pierces the fascia and, by making traction on the excised vein B, the vein B′ can be felt beneath the superficial layer of the deep fascia. This deep fascia is longitudinally incised, the vein B′ is separated from the tissues superficial to it, great care being taken not to disturb the tissues beneath the vein. A large self-retaining thyroid retractor is placed in the wound. Vein B is grasped with a clamp and by distal retraction of vein B′ its undersurface is carefully dissected free. Constant search is maintained for the high-Hunter canal perforator vein and the mid-Hunter canal vein. Whenever the inconstant high-Hunter canal vein is found, it is dissected to its junction with the femoral vein, where it is ligated and excised. The mid-Hunter canal vein, which is usually present, varies greatly in size and length and much diligence may be required to locate it. When discovered it can be grasped with a hemostat and separated from the saphenous vein. The mid-Hunter canal vein is dissected to its approximate junction with the femoral vein where it is ligated and transected. The femoral vein is not usually identified as such, the approximate junction of the mid-Hunter canal vein with the femoral vein being ascertained by feeling the pulse of the femoral artery. The subsartorial vein and the deeper portion of the mid-Hunter canal vein are usually exposed simultaneously. The subsartorial vein should be followed distally as far as is practical, usually from five to seven centimeters, transected and ligated.

Although the sclerosing solution usually controls any bleeding from the subsartorial vein, its efficacy in such control of the proximal end of the cut mid-Hunter canal vein cannot be relied upon, hence the necessity of ligation.

Upon completion of the eradication of the mid-Hunter canal perforator system, the vein B′ is again picked up with a hemostat, and if any portion of this incision remains unexplored, dissection of the vein B′, B″ is carried further caudal, a search being made for any perforating vein that might possibly be present.

If the multiple tourniquet test previously performed indicated no incompetent perforator veins in the lower fourth of the thigh, a Mayo stripper can be applied to the vein B′, B″, and it can be excised by stripping. If, however, previous tests have disclosed the presence of incompetent perforator veins in the vicinity of the adductor tubercle, they must be searched for and eradicated. A longitudinal incision about eight centimeters in length is made over the deep saphenous vein B″ in the vicinity of the adductor tubercle, and this vein is exposed by incising the super-

ficial layer of the deep fascia over it. A search for a perforator vein is instituted in a manner similar to that described in locating the mid-Hunter canal in the midthigh. Once identified, the perforator vein should be followed deeply until point R is exposed. The highest genicular vein, the superior and inferior medial genicular veins of the genicular plexus, and, if present, any tributary making connections with the short saphenous vein, are then followed deeply and ligated near their junctions with the femoral, popliteal, or short saphenous veins.

The next step consists of elimination of varices and incompetent perforator veins in the leg. If the preliminary examination of the patient disclosed no incompetencies of the perforator veins below the knee, varices are removed wherever present. If, however, the multiple tourniquet test demonstrated deficiencis of the perforator veins in this area, the treatment is more complicated. Linton[7] and Warwick[8] pointed out that the perforating veins of the medial aspect of the leg usually make direct and nearly horizontal communications between the deep veins and the saphenous system. For this reason the multiple tourniquet test is valuable in locating the sites of incompetent perforator veins of the leg. Although we have made no exhaustive studies on the leg of the cadaver, surgical dissections have indicated three important locations for deficient perforator veins on the medial aspect of the leg. In order of their frequency they are: 1. From 18 to 22 cm. above the sole of the foot. 2. At about the junction of the upper and lower half of the leg. (Medial margin of the tibia.) 3. At about the middle of the proximal third of the leg. When indicated, these incompetent perforator veins are followed to a point beneath the deep fascia where they are ligated and excised. The rent in the fascial layer is obliterated by appropriate sutures. Whenever the short saphenous vein is found to be incompetent it is ligated and transected at its junction with the popliteal vein. All tributaries within approximately six centimeters of this junction are also ligated. If incompetent perforator veins are found on the lateral aspect of the thigh, they are followed to a point three or four centimeters beneath the deep fascia, within the intramuscular septa, where they are ligated and excised.

Discussion.—Patients who have had one lower limb treated by means of the combined high ligation operative procedure and retrograde injections of sclerosing solution, and the companion extremity treated in the manner described in this paper, observe that the postoperative discomfort is much less noticeable in the latter procedure. This lessening of pain probably results, at least partly, from the fact that the veins, although exposed to the action of the sclerosing solution, are removed and, thus, the usual inflammatory reaction from the injection is avoided.

In the removal of veins so treated, some of the sclerosing solution may remain in the wound, though every effort is made to remove it. In no case did it cause any evident damage. Substantiating this view is the fact that sylnasol, an excellent chemical for sclerosing veins, has also been in-

jected into tissues for treating inguinal hernia without causing appreciable damage to tissue. Indeed, sylnasol is not very different chemically from any other sclerosing soap. In patients who exhibited sensitivity to monolate or similar compounds, the necessary use of quinine hydrochloride and urethane or sugar solutions caused no obvious difficulty.

Insufficient time has elapsed for proper evaluation of the late effects of this procedure. It would appear, however, that the method should reduce the incidence of recurrence. In the entire group of 465 patients, no deaths, massive hematomata or pulmonary embolisms occurred. There were ten mild infections, one rather severe infection and two traumatic cysts. Of these infections only two involved the thigh. The average time of hospitalization was 2.8 days. All patients were walking within 28 hours after operation.

SUMMARY

1. A general scheme of arrangement of the saphenous system in the thigh exists but variations are common.

2. The occurrence of a heretofore unrecognized location of the saphenous vein between the deep fascial layers, of a constant mid-Hunter canal perforating vein at about the junction of the upper and middle thirds of the thigh, and of an inconstant perforator vein connecting with the medial genicular venous plexus and the subsartorial vein is described.

3. Although anatomic variations are common, a definite plan exists, the surgical significance of which is emphasized.

4. Suggestions are made for what appears to be a more effective operative therapy.

Acknowledgment is made to Dr. John B. deC. M. Saunders, Professor of Anatomy at the University of California, for his assistance in confirming the anatomic findings presented in this article.

Acknowledgment also is made to Lt. Comdr. K. A. Tuttle for the financial assistance which made this research possible.

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AN IMPROVED METHOD FOR COLLECTING, CENTRIFUGING AND POOLING BLOOD PLASMA

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CURRENT experimental and clinical publications reveal increasing interest in preserved blood plasma in various forms. The present communication is concerned with the description of a closed method for collecting, centrifuging and pooling blood plasma. Of 23 different types of containers which we devised and tried, the one described here was found most satisfactory.

Description of Container.—We have designed a pyrex glass container which has a capacity of 300 cubic centimeters (Fig. 1A). The bottom, which is rounded off, leads into a narrowly constricted portion having an inside diameter of three millimeters. Below this constriction is a small bulb with a capacity of approximately two cubic centimeters. Below this is a similar second bulb with a small hole through which a needle can be inserted for drawing off the cells from the bottom of the container. At the upper end is a constricted portion, or neck, one centimeter in diameter.

Procedure.—Before use, the container and all other material are cleansed well by means of soap and water, cleaning solution and distilled water. A piece of rubber tubing, (size $\frac{3}{16}$ x $\frac{1}{16}$ inch) one inch (2.5 cm.) long is then drawn over the lower bulb to seal the small hole where the cells are to be drawn off. A vaccine cap is placed over the neck of the container. An air vent (Fig. 2A) is then inserted through the vaccine cap to allow the air within the container to escape while it is being filled with blood. The air vents are made by cutting a glass needle adaptor in half, filling it with cotton and attaching a No. 15 needle (Fig. 2A). A piece of rubber intravenous tubing (Fig. 2B) approximately 15 inches (37.5 cm.) long is then drawn over a No. 15 needle at one end. The other end is fitted over a glass needle adaptor which holds a No. 15 intravenous needle. The end without an adaptor is inserted through the vaccine cap, beside the air vent. The entire set-up is then wrapped and sterilized all assembled.

To collect the blood the patient is placed on the table and the arm prepared and draped in the usual manner. Forty-five cubic centimeters of 2.5 per cent sterile sodium citrate is then drawn into a syringe and instilled into the container, being allowed to run through the tubing (Fig. 2B) through which the blood is to flow into the container. A tourniquet is then applied to the donor's arm and the needle at the end of the collecting tubing inserted into the vein (Fig. 2). The container is held a few inches below the level of the donor's arm to facilitate the flow of blood. It is gently agitated to allow for mixing with the citrate. The container is filled to the top with

blood (Fig. 1B). If two containers are to be filled the tubing leading from the donor's arm is pinched off, the needle withdrawn from the vaccine cap, and inserted through the cap of the second container which may be filled in the same manner. The needle and air vent are then withdrawn from the vaccine cap of the container and a rubber cap drawn over the vaccine cap and neck of the container after it has been cleansed with iodine and alcohol (Fig. 3A).

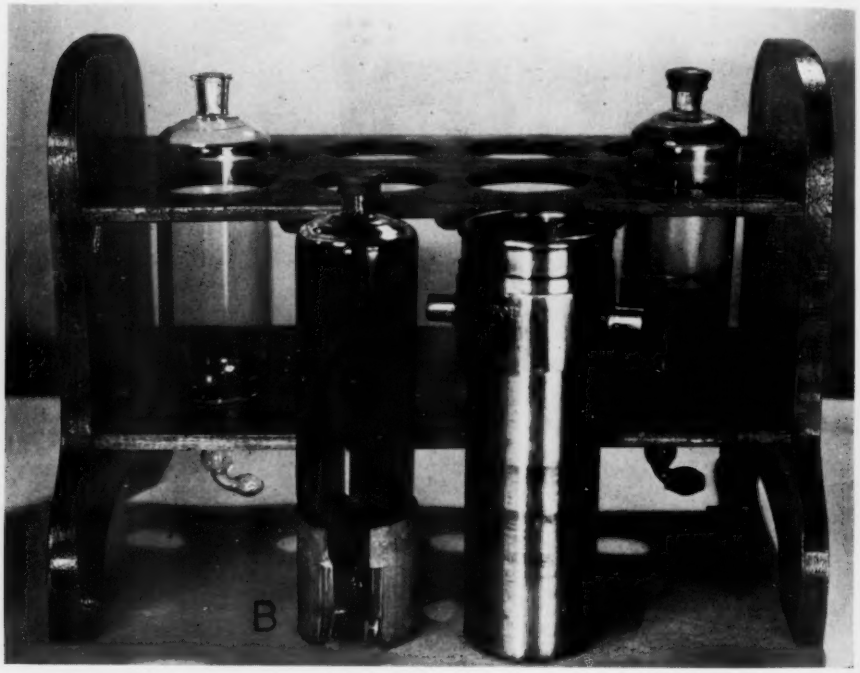

FIG. 1.—A. Empty container showing needle hole in lower bulb for drawing off the cells.
B. Container assembled and filled with blood ready to be placed in trunion cup.
C. Special trunion cup made to receive the container.
D. Container after first centrifugation. Cells separated from plasma. C clamp removed from lower bulb.

The filled containers are now ready for centrifuging. They are placed in especially designed trunion cups (Fig. 1C and 4A) and rotated at 1200 revolutions for 20 minutes. The container is supported by a block of hard wood which is shaped to fit its curved under surface, and prevents the bulbs from touching the bottom of the trunion cup (Fig. 1B). To prevent the force of centrifuging from forcing any blood out around the rubber tubing over the needle hole in the smaller bulb at the bottom of the container, a C clamp (Fig. 1B) is placed over the small bulb and tubing and is tightened against this opening to seal it firmly (Figs. 3A and B). The C clamp is removed after centrifuging is completed. To draw off the packed cells the container is placed in a ring stand (Fig. 4B). The rubber tubing over the smaller bulb is cleansed with iodine and alcohol, and a sterile needle introduced into this bulb through the rubber tubing and needle hole. An air filter is placed through the vaccine cap at the top to allow for fall in

fluid level within the container. The cells may be drawn into physiologic sodium chloride solution and used for transfusing anemia patients.

After the packed cells are all withdrawn, some will be found to adhere to the side of the container. Therefore, the needle is withdrawn, and the container removed from the ring stand. The one-inch (2.5 cm.) piece of

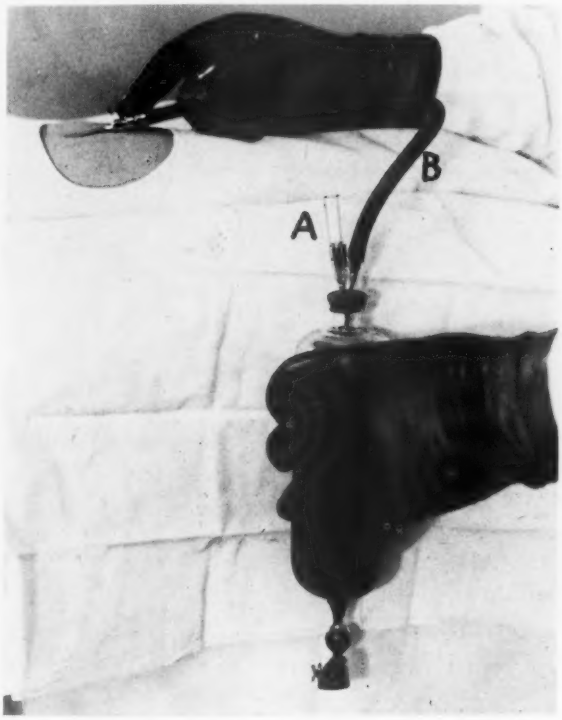

FIG. 2.—Blood from donor being collected into assembled container. A. Air vent. B. Collecting tubing.

tubing over the lower bulb is slightly rotated to bring a new surface of rubber over the hole in the bulb where the needle was inserted for drawing off the cells. The C clamp is again put in place as before, and the container agitated to free the cells adhering to its walls and resuspend them in the plasma. It is again placed in the centrifuge and rotated for ten minutes at 1200 revolutions per minute. This will force the remaining cells into the two lower bulbs. After this second centrifugation the container is turned end for end, so the bulb portion is uppermost, and supported in the ring stand (Fig. 5). The packed cells in the bulbs will not run down through the narrowly constricted portion, but will remain trapped within the two bulbs. The plasma is withdrawn by a needle and air vent being inserted through the vaccine cap, after the cap has been cleansed with iodine and alcohol. The air vent is held above the plasma level as shown (Fig. 5).

When the plasma of six to eight donors is pooled it is placed in the ice box for 12 hours or more. It is finally racked off into sterile physiologic

sodium chloride plus dextrose solution (Fig. 6). During this process it is passed through a 200-mesh filter (Fig. 6A) to remove fibrin clots. A Kaufman syringe serves as a very satisfactory valve for shutting off the flow of plasma when receptacles are to be changed during the procedure.

Discussion.—Many methods have been devised for the separation and pooling of human plasma for therapeutic use. Most previously described methods depend upon siphoning the plasma from a container with a large

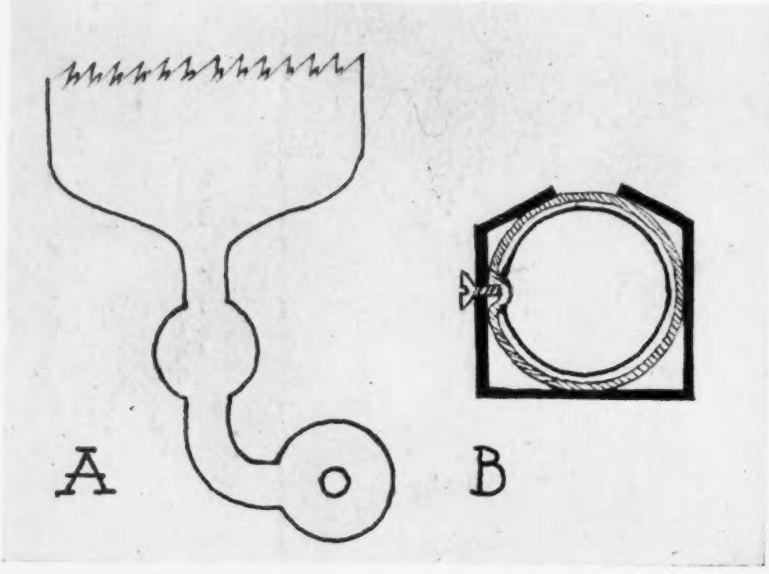

Fig. 3.—A. Diagram of the lower portion of container showing needle hole in lower bulb. B. Cross-section diagram of lower bulb to show how screw of C clamp forces rubber tubing into needle hole to seal it firmly.

plasma-cell interface. Scudder was the first to improve the yield by designing a container with a relatively small area at the junction of the plasma and the cells. Crowley, in 1940, described a container with an even greater reduction in plasma-cell interface. However, this method necessitates the determination of cell volumes on each donor to give a good plasma yield. Furthermore, it presents the difficulty of adequate citration of the blood, and is expensive because each ampoule can be used only once. The separation container which we have designed has been based upon the principle of small plasma-cell interface, but obviates the objections described above.

Some investigators with whom I have discussed this type of container believe that forcing the cells through a narrow constriction by means of centrifugation would tend to rupture many of the cells, and allow their content to flow into the plasma. Experience with this, and similar types of containers, have proven this false. We believe that a clearer plasma is obtained by centrifuging and pooling the plasma the same day than by the commonly employed method of placing the citrated whole blood in the ice box for a period of time and allowing the cells to settle from the plasma by gravity.

SUMMARY

An improved method for collecting, centrifuging and pooling human blood plasma has been described. The yield by this method has been consistently 10 to 15 per cent greater than by any method with which we are familiar. No difficulties are encountered in obtaining satisfactory mixing of the citrate with the blood, cell volumes of donors need not be determined,

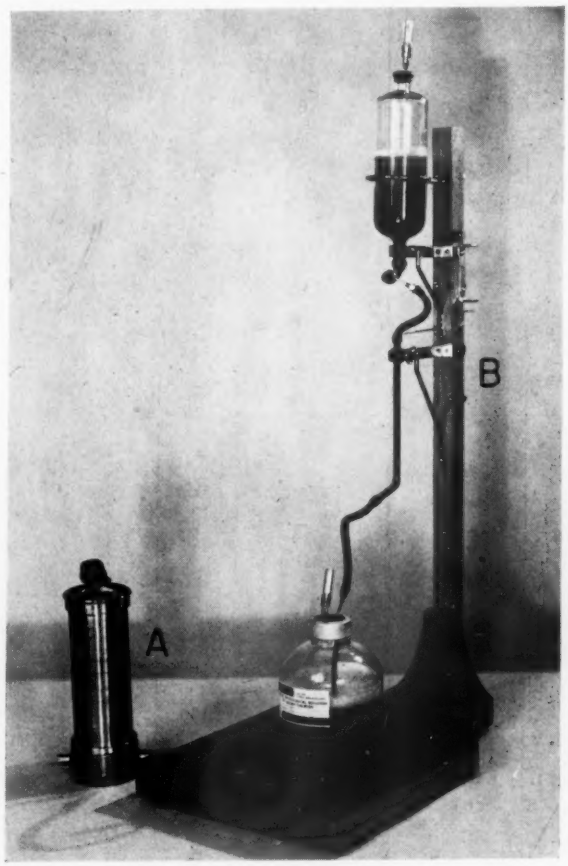

FIG. 4.—A. Trunion cup with container after removal from centrifuge.
B. Container held in ring stand. Needle inserted through rubber tubing over lower bulb for drawing off packed cells. Air vents in place. Plasma is not clear above cell layer because some of cells adhere to sides of container.

and the same container can be used repeatedly. This method requires no containers with a vacuum, as is frequently advocated by other investigators. The method is a completely closed one, and the plasma can be separated and pooled on the same day the blood is collected, with minimal disintegration of red blood cells during the procedure. The blood cells can easily be preserved for transfusing anemia patients. The same principle could be used in designing containers to hold a larger volume of blood.

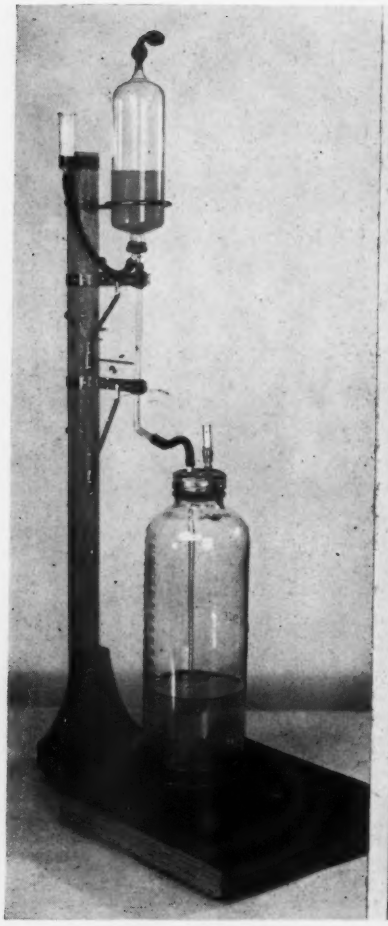

FIG. 5

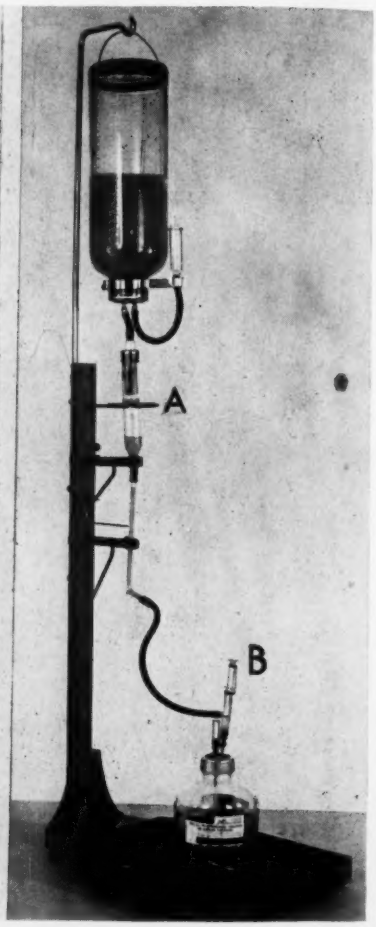

FIG. 6

FIG. 5.—Plasma being drawn off into pooling bottle. Air vents in place. Blood cells trapped in bulbs at upper end of container.

FIG 6.—Plasma being drawn from pooling bottle into smaller flasks. A. Filter. B. Kaufman syringe.

Acknowledgment is made to Doctors Lindsey F. Cocheu and Donald E. Brace, of the Flower and Fifth Avenue Hospitals, New York City, for their interest, many suggestions and generous supply of bank blood and donors. We, also, wish to thank Doctors Charley J. Smyth and S. E. Gould of the William J. Seymour Hospital, Eloise, Michigan, for obtaining materials, blood donors and financial assistance. Also, thanks to the E. Machlett and Son Company, New York City, for their splendid co-operation in producing the necessary glassware.

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THE PERIPHERAL CIRCULATION DURING THE TOURNIQUET SHOCK SYNDROME IN THE RAT*

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AMONG RECENT INVESTIGATIONS on circulatory failure in tourniquet shock, at least two have dealt with microscopic observations of the mesenteric blood vessels remote from the site of the damage inflicted.[1, 2] These observations were confined to changes in caliber of the vessels and rate of the blood flow. The capillaries were referred to, but in neither paper was consideration taken of the possibility that the capillary bed possesses several vascular components, each playing a specific rôle in the functional activity of the capillary bed as a whole.

This aspect of the capillary bed and the significance of its specific reactions have been recently worked out in detail for the normal mesenteric circulation of the dog and rat.[3] Moreover, the observed reactions have proven to be sufficiently critical for use in following the progressive changes caused by hemorrhage and in enabling one to distinguish the effects of acute[4] from those of graded hemorrhage.[5]

The application of a tourniquet to an extremity and its subsequent release is a method of inducing, with a minimum of direct trauma, a considerable reduction in blood volume through the loss of fluid into the damaged limb (Wilson and Roome[6]). Some investigators have attributed the resulting shock syndrome and eventual death of the animal mainly to the fluid loss.[7, 9] Others have indicated that the syndrome includes either the presence of a toxic favor[10, 11, 12] or the absence of some ingredient of the blood lost to the damaged tissue.[13]

The sensitive responses of the capillary bed offer a method of distinguishing between the mechanical effects of fluid loss and the toxic effects of abnormal conditions in the blood stream.[16] Furthermore, the responses of the peripheral circulation, since they deal with the components of the vascular system with

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and New York University. It was also supported in part by the Lilly Research Laboratories, Woods Hole, Massachusetts. It constitutes the sixth of a series of studies on experimentally induced shock. The first study is listed as No. 3, the third as No. 14, the fourth as No. 4 and the fifth as No. 5 in the bibliography of the present paper. The second study, on the Noble-Collip rotating drum trauma, appeared in Am. J. Physiol., **139**, 123, 1943.

which the circulatory failure is primarily concerned, make it possible to determine the relative importance of these two factors in the syndrome.

This paper deals with a microscopic study of the circulatory changes in the meso-appendix of the rat under nembutal anesthesia, after the release of a tight tourniquet placed around the thigh for a protracted period of time.

METHOD

The rats varied in weight from about 150 to 200 Gm. In most of the experiments the tourniquet was applied to one hind limb only, a rubber band being wrapped as high as possible around the thigh to occlude all flow without thrombosing the blood vessels. This was done on the unanesthetized rat held in a specially constructed cage, for which we are indebted to Dr. F. M. Allen. About half an hour before release of the tourniquet, the rats were given an intramuscular injection of sodium pentobarbital (2–3 mg./100 Gm. body-weight), known commercially as nembutal. The meso-appendix was then exposed for microscopic observation. The peculiar advantage of the meso-appendix for a study of the capillary bed has been presented in our recent paper,[3] together with means for minimizing the effects of the operation involved in the exposure. The essential precautions are minimum handling of the intestine and constant irrigation of the exposed tissue with warm gelatin-Ringer's solution.* When properly prepared the tissue is servicable for continuous observation over a period of several hours.

Simultaneously with the observations on the meso-appendix, blood pressure determinations were periodically made by using a pneumatic rubber cuff around the thigh of the limb not subjected to the tourniquet.[14] Hematocrit readings by the Van Allen method were also taken.

Prior to release of the tourniquet, the meso-appendix was always examined to establish the normality of its circulation. The chief criteria of normality were (a) a relatively sporadic flow in the capillaries and a restriction of most of the blood to the central channels leading from the arterioles to the venules; and (b) a general, nondilated state of the muscular vessels of the bed. A good test for the normal state was the application of a few drops of histamine in gelatin-Ringer's solution (1:10,000 to 1:100,000) to the surface of the meso-appendix. This should produce a temporary dilatation of the vessels and an appreciable increase in the extent of the capillary flow. If the trauma incidental to handling the intestine has been excessive, the vessels already will have been dilated to the extent that the effect of the histamine at this concentration will be negligible.

The criteria[5] for noting the progressive changes in the circulation following release of the tourniquet were: (a) Changes in the distribution and rate of flow in the capillary bed; (b) changes in caliber of selected arterioles (15–20 micra in diameter); (c) augmentation or diminution of the vasomotion

* This had the following constitution in grams-per cent in water: Granular ash-free gelatin, 1; NaCl, 0.8; KCl, 0.02; $CaCl_2$, 0.02 and $NaHCO_3$ sufficient to bring the solution to p_H 7.2–7.4.

of the metarterioles;* and (d) change in the reactivity of the metarterioles to the local application of epinephrine. This last criterion was tested by determining the minimal concentration of epinephrine required to produce a partial narrowing of the muscular components of the capillary bed. In normal rats, anesthetized with a minimum effective dose of sodium pentobarbital, this was 1 part epinephrine in 1 million or in 2 million parts gelatin-Ringer's solution.

EXPERIMENTAL RESULTS

The tourniquet was applied to one hind limb for periods of 3, 5, 7 or 8 hours. In two cases the tourniquet was applied to two hind limbs for 5 hours. Only those rats were considered in which release of the tourniquet was followed by a return of the circulation in the occluded limb. The accompanying table gives the number of rats studied, the survival time and the percentage of fatalities in each group of the several periods with one-limb tourniquet (Table I).

TABLE I

No. of Rats	Time in Hours of Tourniquet Application	Survival Time in Hours of Fatal Cases after Tourniquet Release	No. of Fatal Cases
9	3–4	4–5	3
38	5–6	3.5–4	29
6	7	2.5–3	5
3	8	2–2.5	3

After removal of the tourniquet, changes appeared in the circulation of the meso-appendix, which could be classified into three successive, well-defined stages: An initial hyperemic; an hyperreactive; and an hyporeactive stage. The duration and intensity of the changes and the relative lengths of the stages were found to vary with the duration of the period of tourniquet application. The following is a summarized description of the effects observed:

Tourniquet Applied for Three to Four Hours

(9 rats, of which 3 succumbed)

1. *Initial Hyperemic Stage* (duration, 20–30 minutes after tourniquet release).—Within a few minutes after release of the tourniquet, the blood pressure fell precipitously from 120 Mm. to about 80 Mm. Hgs and then slowly rose after 4 to 5 minutes until, within 30 minutes, it had reached about 100 Mm. During the abrupt fall, the heart rate was considerably slowed.

In the meso-appendix the release was followed within one to two minutes by a marked dilatation of all the muscular vessels, especially noticeable in the larger arteries and veins (100–150 micra), which dilated to about one-

* The metarterioles are the terminal, discontinuously muscular vessels leading from the arterioles and constitute the proximal segment of the central channels in the capillary bed. The metarterioles and their precapillary offshoots normally exhibit a vasomotion consisting of alternating constrictor and dilator phases at irregular intervals of 30 seconds to 3 minutes. (Refer for further details to reference 3).

half more than their original diameters. The vasodilatation was accompanied by a change of the normally restricted capillary circulation to an over-all hyperemic state, with a significant slowing of the flow, especially on the venous side of the capillary bed.

This stage lasted about 20 to 30 minutes, and the hyperemia passed off as the blood pressure began to rise with appreciable acceleration of the blood flow in the capillary bed.

Leukocytes were seen sticking in increasing numbers to the inner walls of the capillaries and venules. Further evidence that the endothelial walls were being affected at this stage was the formation of minute petechiae with extravasation of red cells in some areas of the capillary bed.

2. *Hyperreactive Stage.*—About 30 minutes after release of the tourniquet the blood pressure again began to fall, but this time gradually and to a level as low as 60 Mm. Hg. This was accompanied by a progressive swelling of the damaged limb over a period of about two hours.

The arteries and veins underwent a continually increasing constriction until, at the time of the maximal swelling of the damaged limb, they had been reduced to about one-third their original diameters. The two outstanding reactions in the capillary bed were an augmentation of the vasomotion and an hyperreactivity of the vessels to the topical application of epinephrine. The vasomotion of the metarterioles and precapillaries became increasingly frequent and pronounced. This restricted the flow to the central channels so that the true capillaries became relatively anemic. The hyperreactive condition was indicated by the fact that epinephrine in concentrations as low as 1:10 million to 1:20 million caused an immediate constriction of the metarterioles, whereas, a similar reaction prior to removal of the tourniquet could be obtained only with a concentration of 1:2 million. This hyperreactivity persisted for almost three hours. The blood pressure had now fallen to 60–65 Mm. Hg and the flow through the capillary bed was considerably slowed, especially on the venous side of the bed. Hematocrit values of blood samples obtained from the jugular vein of the fatal cases reached 55 to 60 per cent.

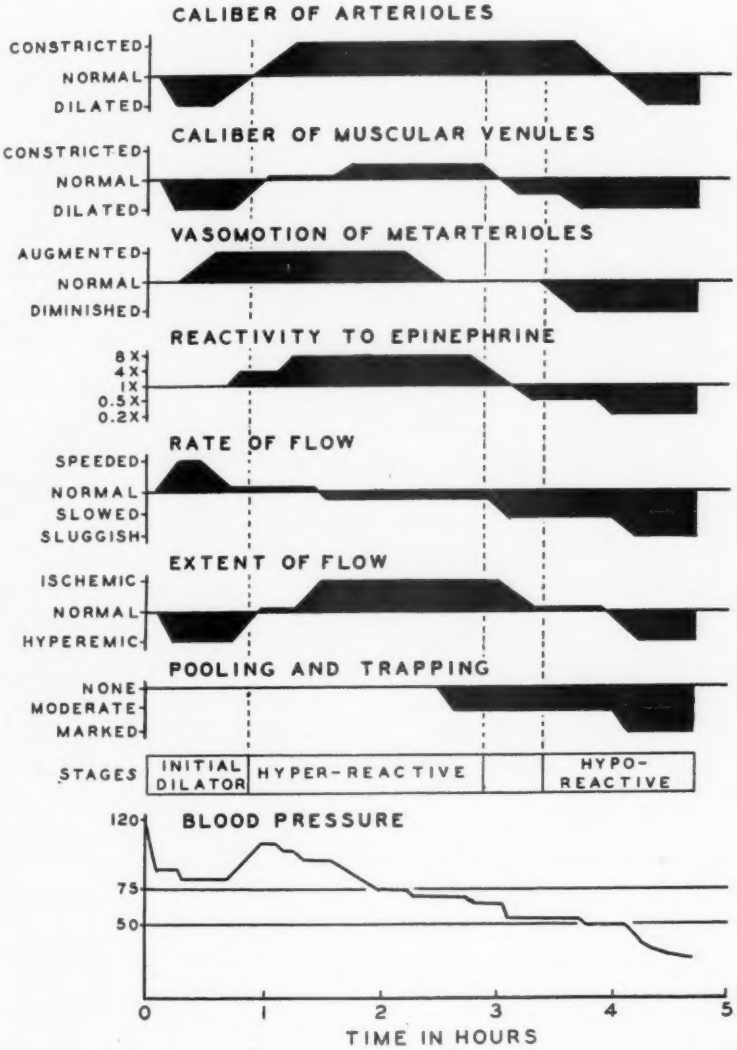
Except for the hemoconcentration, the reactions of the capillary bed throughout this period, *viz.*, constriction of the larger vessels, augmented vasomotion of the metarterioles and hyperreactivity to epinephrine, were similar to those occurring in acute hemorrhage.[4]

In the six rats which eventually recovered, the normal unidirectional flow through the bed, although considerably slowed, was never lost. The circulation through the bed began to improve and the blood pressure returned to normal within four to five hours after release of the tourniquet.

In the three rats which did not recover, the flow in the capillary bed became increasingly sluggish while much of the blood by-passed the bed through arteriovenous anastomoses. The blood pressure continued to fall and, at about 50–60 Mm. Hg., there developed an increasingly persistent backflow from the venules into the capillary bed. The consequent pooling and stagnation of blood in the capillaries resulted in an abrupt collapse of the peripheral circulation and, within five to ten minutes, was followed by

CHART I

CHANGES IN CAPILLARY BED
AFTER RELEASE OF 5 HOUR TOURNIQUET



death of the animal. During this entire period the epinephrine reactivity remained hypernormal, both in the rats which eventually recovered and in those which succumbed, the reactivity in the latter persisting until a few minutes before death.

No definite hyporeactive stage appeared in this group.

Tourniquet Applied for Five to Six Hours

(38 rats, of which 29 succumbed)

A tabulation of the reactions taken from the protocol of a rat typifying the effect of a five-hour tourniquet is given in Chart 1. The following is a general summary of the reactions of the rats of this group:

1. *Initial Hyperemic Stage* (duration 30–40 minutes after tourniquet release).—This period of hyperemia and vascular dilatation was similar to that described in the preceding experiment except that it was more intense and of longer duration. Pronounced leukocytic sticking lasted for 20 to 30 minutes and was accompanied by the appearance in the circulation of small clumps of red and white cells. These emboli frequently plugged vessels in the capillary bed but soon were dislodged as the general hyperemia persisted. The swelling of the damaged limb began before the initial hyperemic stage had disappeared.

2. *Hyperreactive Stage.*—The development of an hyperreactivity occurred before the initial hyperemic stage had passed off. This could be detected by the augmentation of the metarteriolar vasomotion and the appearance of an increased reactivity to epinephrine, while the larger vessels were still dilated and the capillary flow was hyperemic.

A well-defined hyperreactive stage, with a generalized ischemia and a slowed capillary flow, became evident within an hour and a half after release of the tourniquet and lasted for about 45 to 60 minutes. The flow in the capillary bed became considerably slowed before the blood pressure had fallen to 55 to 60 Mm. Hg. Hematocrit values attained 60 per cent.

3. *Hyporeactive Stage.*—A change to the hyporeactive condition began to develop while the capillary flow was still unidirectional, although becoming increasingly sluggish. The epinephrine reactivity fell below normal and vasomotion of the metarterioles disappeared while the arterioles were still partially constricted. The capillaries, which prior to this were anemic, now began to contain blood throughout the bed.

In the 29 rats which eventually died this was followed several minutes later by a dilatation of the muscular metarterioles and precapillaries of the bed. A backflow from the venules developed, still further filling the capillaries with static blood. By this time the blood pressure had fallen below 40 Mm. and death generally occurred about 4.5 to 5 hours after release of the tourniquet.

Throughout the hyporeactive period, the larger arteries and veins remained constricted as in the hyperreactive stage. Dilatation of these larger vessels was a terminal phenomenon and occurred only 15 to 20 minutes before death.

Of the nine rats which survived, the circulation never went beyond the initial phase of the hyporeactive stage. The critical features for survival appeared to be the persistence of a unidirectional flow and the resumption of vasomotion after a transient cessation of not more than 20 to 40 minutes.

Tourniquet Applied for Seven to Eight Hours
(9 rats, all of which succumbed)

The initial hyperemic dilator stage appeared immediately after release of the tourniquet and was followed within a few minutes by a slowing of the blood flow. The swelling of the damaged limb appeared early and was accompanied by a partial constriction of the larger arteries. Hemoconstriction was moderate, the hematocrit values not exceeding 50 per cent. The initial dilator stage, with normal reactivity to epinephrine, lasted at least 45 to 50 minutes and in the eight-hour tourniquet experiments approached two hours. The hyperreactive period was not prominent, and, especially in the eight-hour experiments, the initial dilator stage passed directly into the hyporeactive stage, the reactions of which were more profound than those in the five- to six-hour experiments. The capillaries became markedly congested with widespread vasodilatation, and death occurred within two to three hours after release of the tourniquet.

The failure of the circulation to return to the damaged limb after release of the tourniquet occurred more frequently when the tourniquet was applied for more than six hours. Rats in which this occurred showed none of the circulatory changes described above.

Tourniquet Applied for Five Hours to Two Hind Legs

Only two rats were treated in this manner. The initial hyperemic dilator stage developed within one minute after release of the tourniquets and disappeared 10 to 15 minutes later. Swelling of both legs became appreciable before the hyperemic stage had disappeared. During this period there was a marked vasoconstriction of the arteries and arterioles and a pronounced vasomotion of the metarterioles. The epinephrine reactivity rose from 1:2 million to 1:10 to 15 million and persisted until a few minutes before death, 2.5 to 3 hours after release of the tourniquet. Except for the initial dilator stage and the subsequent hemoconcentration, the reactions of the capillary bed closely resembled those of severe acute hemorrhage.

Discussion.—The two factors to which the changes in the tourniquet shock syndrome have generally been ascribed are fluid loss and the elaboration of so-called toxic substances. Our experiments have shown that the peripheral circulatory collapse can occur either with both factors contributing significantly or with one or the other predominating, the relative effectiveness of the two factors varying with differences in the duration of the application of the tourniquet. The shorter the duration, the more predominant were the mechanical effects of fluid loss and the less were the indications of a toxic factor. On the other hand, the longer the duration of the tourniquet, within limits, the more predominant were the toxic manifestations.

The five- to six-hour period of applying the tourniquet to one hind limb

produced changes in the visceral vascular bed which most nearly approached those observed in irreversible hemorrhagic shock.[5] These were an hyperreactivity followed by an hyporeactivity of the capillary bed. The initial hyperemic stage appears to be peculiar to the tourniquet type of shock.

Of special interest in tourniquet shock is the difference between the circulatory reactions immediately following release of the tourniquet and those appearing in the later stages of the shock syndrome. Both are dilator responses of the muscular vessels of the capillary bed but, whereas, the first is accompanied by a developing hyperreactivity, the latter is associated with a definite hyporeactivity of the vessels. Both reactions are undoubtedly related to changes which occur in the damaged limb: The first appears after a period of tissue anoxia and some muscle damage caused by the pressure of the tourniquet cord; the second, after the fluid loss into the limb.

The initial dilator stage occurred in all the rats, irrespective of whether they died or survived, while the latter typically appeared only in rats which eventually succumbed.

Initial Hyperemic Stage and Hemoconcentration.—Immediately following removal of the tourniquet, the reactions of the vessels in the meso-appendix suggest the release of dilator substances into the blood from the damaged limb. These, although temporary in their effect, may predispose the blood vessels to the development of the hyporeactivity which appears later. The effect of the initial dilator phase and the hemoconcentration, with the resulting increased viscosity of the blood, in tourniquet shock, may explain the reduction in flow through the capillary bed at an earlier stage of hypotension than that which obtains after hemorrhage.[5] Thus, an animal in hemorrhagic hypotension with a blood pressure of 60 Mm. still has an adequate though markedly slowed peripheral circulation. On the other hand, at a similar blood pressure level in tourniquet shock the capillary circulation is usually on the verge of becoming disrupted.

Hyperreactive Stage.—This stage in the tourniquet experiments, except for possible subsidiary effects of hemoconcentration and the initial and transitory dilator reaction, resembled that found early in rats subjected to hemorrhage.[4, 5] In the three- to four-hour tourniquet experiments this type of hyperreactivity predominates throughout. Fatality is low and, in the rats which succumb, the collapse of the circulation can be ascribed primarily to the mechanical effect of the fluid loss.

The mechanical effect was found to be still more predominant when two limbs were ligated. Considered superficially, it would seem that damage to a larger mass of muscle should predispose the animal to a more toxic type of shock. However, two limbs also offer a larger site for fluid loss. The fluid lost is excessive and the consequent hyperreactivity continues until the rats die from the mechanical effects of circulatory collapse before the development of hyporeactivity.

Hyporeactive Stage.—Our observations on complete tourniquets and those of Page and Abell[2] on venous tourniquets agree regarding the development and persistence of vasoconstriction of the larger blood vessels throughout

most of the syndrome. However, our observations lead us to infer that, accompanying the widespread peripheral ischemia, the capillary circulation develops an autonomy and reacts differently from the remainder of the circulatory system. This is indicated by the fact that the muscular vessels of the capillary bed, as seen in the meso-appendix, relax while the larger vessels do not.

The independence of action of the capillary bed seems to be related to conditions developed in the ischemic tissues. These conditions would appear to serve as a local mechanism for increasing blood flow to the tissues. However, at this stage of the shock syndrome the circumstances of diminished blood volume and low blood pressure are such as to allow of no significant increase in flow. As a result, therefore, the hyporeactive state of the capillary bed eliminates its compensatory action against fluid loss and thus negates the compensatory effect of the widespread vasoconstriction elsewhere. The actual amount of blood which is present in the peripheral vessels may be less than in normal animals, as Fine and Seligman[15] have shown, but the blood which reaches the bed becomes pooled there. This aggravates the general oligemia and contributes to the circulatory collapse. The late dilatation of the arteries in the cat's mesentery described by Page and Abell[2] occurs only in the terminal stages of the collapse and is not to be confused with the hyporeactivity in the capillary bed which appears earlier.

One of the chief features in the development of the hyporeactive stage is a long-continued maintenance of a much slowed peripheral circulation. This stage tends not to occur after a relatively short tourniquet application to one hind limb or after a longer application to two hind limbs. The slowing of the peripheral flow resulting from application of the tourniquet to one hind limb for a relatively short period of time (three to four hours) usually is insufficient to cause circulatory collapse. The condition resembles that of moderate acute hemorrhage. The few rats which succumbed were probably highly susceptible to fluid loss. Susceptibility of this sort is discussed in a previous paper.[5] When two hind limbs were occluded, even for relatively long periods, the condition resembles that of severe acute hemorrhage. The fluid loss is so great as to induce circulatory collapse while the capillary bed is still in the hyperreactive state. A tourniquet application of five to seven hours to one hind limb is the optimum treatment for inducing a well-defined hyporeactive stage following the hyperreactive stage.

Since the reactions were observed in the meso-appendix remote from the site of the inflicted injury and since they occurred only if the circulation was reestablished and was maintained for a protracted period of time, it is logical to infer that, at least one of the factors responsible for the observed effects is the transmission of a substance or of substances from the damaged limb. Objective evidence for the presence of such substances in the blood of shocked animals has been presented in a preliminary paper.[16] The relation of these substances to those producing the toxic effects obtained in dogs by Blalock,[12] and Katzenstein, Mylon and Winternitz,[10] is not clear. Both of these investigations were conducted by noting the effect of the intravenous injection

into normal dogs of thoracic lymph obtained from injured dogs. Blalock performed crush injuries on one hind limb of dogs under either morphine or nembutal and collected the lymph for hours before and after the injury. Some of the recipient dogs died, a few with a significant fall in blood pressure and a few with casts in the urine. Katzenstein, Mylon and Winternitz used complete tourniquets on two hind limbs of dogs anesthetized with nembutal. The injection of lymph from these dogs (time of obtaining not recorded) produced a blood pressure fall in nine out of 18 recipient dogs. In our experiments a prime feature for ascertaining the existence of a so-called toxic factor was the change in reactivity of the capillary bed in which the vascular components become functionally depressed.

Allen[11] observed that, the longer the period of tourniquet application, the more difficult it was to save the animal by fluid therapy. He intimated that the development of a toxic factor would help to explain the fatal results of prolonged tourniquet application. However, he stressed the fluid loss factor because the fatal results obtained by ligating a larger muscle mass (*e.g.*, two hind limbs) frequently could be avoided, by fluid therapy alone. Actually, the animals subjected to a one hind limb tourniquet should not necessarily be compared with those subjected to tourniquets on two or more hind limbs. The fact that Allen found the latter to be amenable to fluid therapy supports the view that their death is due chiefly if not entirely to excessive fluid loss.

An alternative to the presence of a toxic factor has been presented by Selye and Dosne[13] from their experiments on tourniquet shock in monkeys and cats. They found that damaged tissues utilize certain substances (*e.g.*, sugar) more actively than the corresponding normal tissues. They suggested that the symptoms following release of the tourniquet are "not because substances coming from the limb poison the rest of the body but because active metabolic processes drain the body of certain essential compounds, the lack of which causes shock."

Selye and Dosne also tested for the presence of toxic substances in the blood from the damaged extremity by injecting the blood into adrenalectomized rats. By using death-rate as a criterion they found no difference between this and the blood of normal animals. From this they concluded that no special toxicity could be demonstrated in the blood derived directly from a leg so severely damaged by anoxia that, had its circulation been reunited with the rest of the body, severe shock would have developed.

Adrenalectomized rats are known to be highly sensitive to a variety of toxins. We have found (unpublished observations) that such rats are not suitable for testing substances which depress the peripheral circulation since the operation alone causes the capillary bed to become hyporeactive to epinephrine and to exhibit no vasomotion. This would render such rats inadequate as tests for substances which induce hyporeactivity of the capillary bed, since the response to be looked for is already present in the test animal.

Evidence for a toxic factor in traumatic shock has generally been obtained from animals anesthetized during the procedure of inducing the shock. Katzenstein, Mylon and Winternitz[10] have indicated that the dosage of

nembutal must be carefully controlled to minimize the vasodepressor effect of the drug. In the experiments described in this paper the rats were not anesthetized for the tourniquet application but only for the exposure of the meso-appendix, a single minimal effective dose of nembutal being administered shortly before exposing the meso-appendix. The subsequent comatose state of the animals during the shock syndrome obviated further medication. Even with such precautions it is to be expected that the anesthetic will exert some effect. Fine and Seligman[15] stress this feature and claim that morphine (3 mg./Kg.) does not have the deleterious effects of typical anesthetics. In defense of our use of sodium pentobarbital it may be stated that in our experiments on graded hemorrhage in dogs[5] the capillary circulation of the omentum exhibited the same succession of events (hyperreactivity followed by hyporeactivity) irrespective of whether the dogs had been immobilized with morphine or with the barbiturate. In a recent paper[17] we have presented the effects of different anesthetics on the capillary circulation in the omentum of hemorrhaged dogs. With sodium pentobarbital the effects were more marked and appeared earlier in the hemorrhagic syndrome than when morphine was used. However, the succession of events was identical and the hyporeactive stage of the capillary bed developed under both types of treatment.

SUMMARY

During the shock syndrome after release of a tourniquet applied to one hind limb for five to six hours, the peripheral circulation in the rat's meso-appendix undergoes the following changes, provided circulation returns to the limb: These changes are classified into three successive stages:

I. *Initial Dilator.*—The initial dilator stage appears within a few minutes after release of the tourniquet and is more prominent the longer the tourniquet has been applied. It is characterized by (1) abrupt fall of blood pressure followed by a rise which does not reach normal levels; (2) widespread vasodilatation and hyperemia with slowed capillary flow; (3) leukocytic sticking and development of minute extravasations observed in the capillary bed; (4) normal reactivity of the capillary bed to the topical applications of epinephrine; and (5) in most cases, persistence of the vasomotion of the metarterioles.

II. *Hyperreactive.*—The hyperreactive stage appears when the damaged limb begins to swell. The following changes are commensurate with the extent of swelling: (1) Continued fall in blood pressure; (2) increased hemoconcentration and further slowing of the capillary flow; (3) hyperreactivity to epinephrine; and (4) widespread vasoconstriction of the larger vessels and augmented vasomotion with restriction of the capillary flow to the central channels of the capillary bed.

III. *Hyporeactive.*—The hyporeactive stage appears proportionately earlier the longer the tourniquet has been in place. It is characterized by (1) fall in blood pressure to below 60 Mm. Hg., (2) hyporeactivity of the capillary bed to epinephrine; (3) complete loss of vasomotion; and (4) over-all sluggish capillary flow followed by stagnation, venular backflow and finally a collapse of the circulation.

When the tourniquet has been applied for three to four hours the capillary bed maintains its hyperreactive state throughout. The rate of capillary flow becomes greatly reduced but in the majority of cases, the normal directional flow is maintained and the circulation progressively improves. In the few cases which succumb, the hyperreactivity persists to within a few minutes before death.

When the tourniquet has been in place for six hours, or longer, there is a tendency for the hyperreactive stage to be shorter, the longer the duration of the tourniquet application. In some cases, the initially hyperemic capillary bed with its dilated vessels may pass directly into the hyporeactive phase.

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PROPOSED ALTERATION IN THE KNEE JOINT OF PROSTHESIS FOR BELOW-KNEE AMPUTATION

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THE PURPOSE of this paper is to point out certain facts that were observed while treating a patient with an infection of a below-knee stump. The patient, an officer in the Air Corps, received a G. S. W. of the right leg in August, 1942, which necessitated a below-knee amputation, leaving a four-inch tibial stump. He was fitted with a prosthesis and was able to walk without any appreciable limp. He stated, however, that while flying a plane or driving a car there was an excessive amount of pressure and irritation to the anterior tip of the stump. This resulted in so much pain at times that he would have to turn over the controls to his copilot or suffer considerable pain for the following 24 to 48 hours. Several attempts at readjustment of the leg by the manufacturers did not alter the situation.

In order to visualize the true nature of the patient's complaint roentgenograms were taken with the prosthesis in place (1) with weight-bearing; (2) nonweight-bearing; knee extended; and (3) nonweight-bearing and knee flexed. Figure 1 is a tracing of the roentgenogram taken in position 3, *e.g.*, nonweight-bearing and knee flexed.

It is at once obvious that any attempt to extend the prosthetic leg would cause practically all of the pressure to be exerted at point E (Fig. 1). The reason for this is likewise obvious when lines A–B and C–D are superimposed on the drawing. These lines represent the long axes of the prosthetic leg and the stump, respectively. The prosthetic leg is flexed 90°, whereas the tibial stump is only flexed 60°–70°. This, in turn, is caused by the fact that the axis of the prosthetic joint is distal to the axis of the knee joint. Consequently, during the process of flexion the prosthetic joint swings through an arc of 90°, while the stump is only allowed to swing through an arc of 60°–70°. Thus, instead of the long axes of the stump and prosthesis remaining parallel they become angulated and an excessive pressure is brought to bear at point E where the front end of the stump contacts the anterior surface of the prosthesis.

Having analyzed the cause of the unequal distribution of pressure on the end of the stump, it would seem a very easy matter to correct the fault by merely changing the position of the axis of the prosthetic joint to coincide with that of the knee joint proper. That the solution to this problem is not quite so easy will be illustrated by studying Figures 2 and 3. Figure 2 is a tracing of a roentgenogram with the knee extended and the patient bearing weight on the leg. Figure 3 is a similar tracing without weight-bearing. Note that in Figure 2 the axes of the prosthetic knee joint and that of the

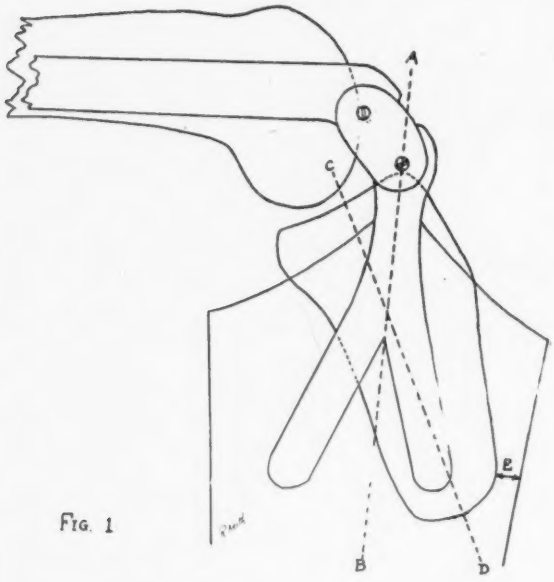

FIG. 1

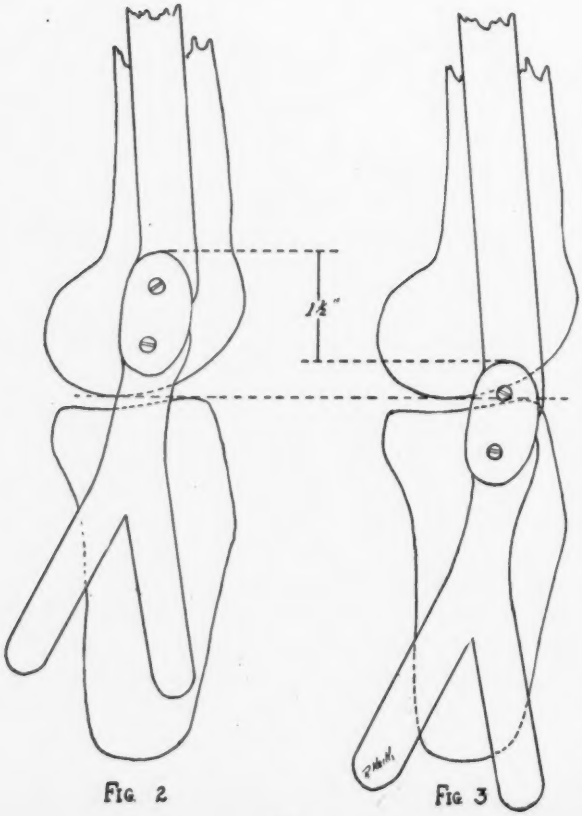

FIG. 2

FIG. 3

knee joint proper are approximately superimposed. When weight is removed from the prosthesis the prosthetic joint (along with the entire prosthesis) slides distally 1.5 inches (see Fig. 3), throwing the two joint axes out of alignment. It is in this latter position of malalignment that one finds the prosthesis when flexion is required. Compare the relative positions of the prosthetic joints in Figures 1 and 3.

The fact that the prosthesis slides distally when there is no weight-bearing is not due in any way to an improper fit. It must be remembered that weight-bearing with this type of prosthesis is transmitted to the upper thigh and tuberosity of the ischium. When the weight is borne on the prosthesis

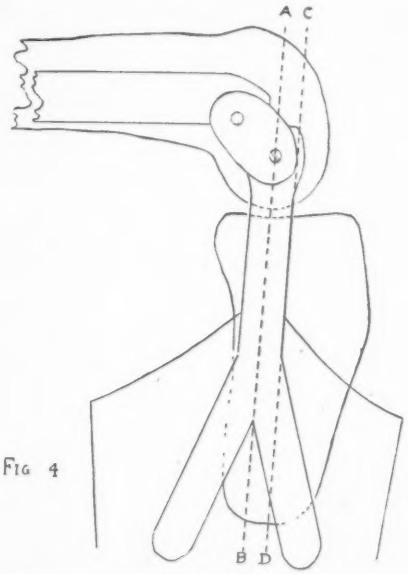

FIG 4

there is considerable give and compression of the soft tissue in the region of the weight-bearing surfaces. The soft tissue compression in this patient amounted to 1.5 inches. Consequently, when weight is removed from the prosthesis, no matter how perfect the fit, it slides off the thigh distally.

One solution to the problem would be to alter the position of the prosthetic joint to a higher level by shortening the upper brace 1.5 inches and lengthening the lower brace a similar amount. Thus, during weight-bearing the axis of the prosthetic joint would lie 1.5 inches proximal to that of the knee joint proper, but when weight was removed the prosthesis would slide distal, and the two joints' axes would for all practical purposes coincide.

Figure 4 is a tracing of a model so designed. It will be noted that the long axes of both stump (C–D) and prosthesis (A–B) are parallel. The tibial crest is parallel to the front of the prosthesis, thus, giving a broad pressure-bearing surface instead of a pressure point, as in E (Fig. 1). This is not a satisfactory solution, however, because the lower brace is so long the stump and prosthetic socket nearly disengage during flexion.

We now have the two factors of the problem which must be dealt with: (1) Under conditions of nonweight-bearing the joint axes of the artificial leg and the knee joint proper must approximate a common plane; this plane must be at right-angles to the long axis of the femur. (2) The leg portion of the prosthesis must not be allowed to slide off the stump during flexion.

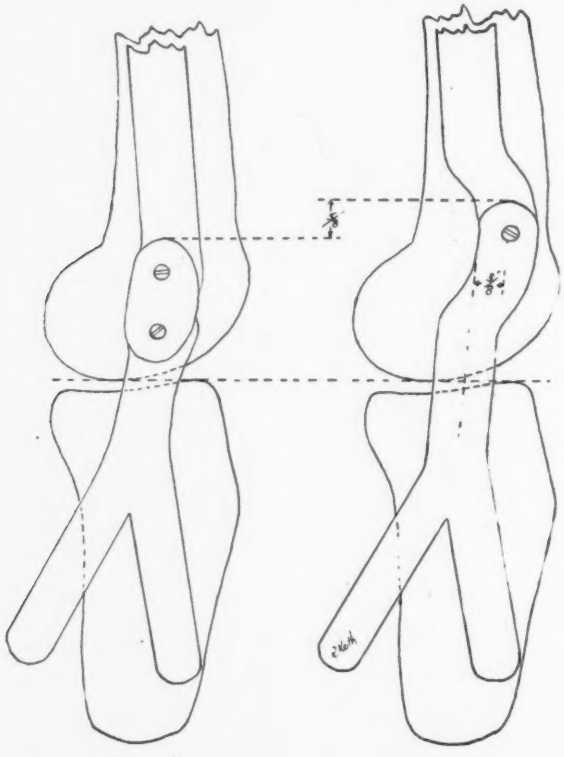

FIG. 2 FIG. 5

Models were made and, after considerable experimenting, a joint was devised that would fulfill the above requirements. For the purpose of this paper details of the actual joint mechanism are irrelevant. Suffice it to say that it is of a simple hinge variety whose axis is offset 3/8 inch anterior to the long axis of the brace. (See Fig. 5.)

Figure 5 is a tracing of the proposed model joint superimposed on the roentgenogram tracing of the patient's knee. This is the position of the joint during weight-bearing. Compare this with the position of the old prosthetic joint during weight-bearing. For convenience, Figure 2 has been reproduced beside Figure 5. Note in Figure 5 that the joint has been raised 5/8 inch, but that the overall length of the brace is the same. Also note the 3/8-inch anterior offset of the prosthetic joint axis.

When there is no weight-bearing on the prosthesis it slides distally 1.5 inches, as explained previously, thus bringing the prosthetic joint down to lie in the desired plane as illustrated in Figure 6. (Compare Figs. 5 and 6.)

Figure 6 shows the position of the prosthetic joint without weight-bearing when flexion would be desired. It is the same relative position as that of the joint in Figure 7.

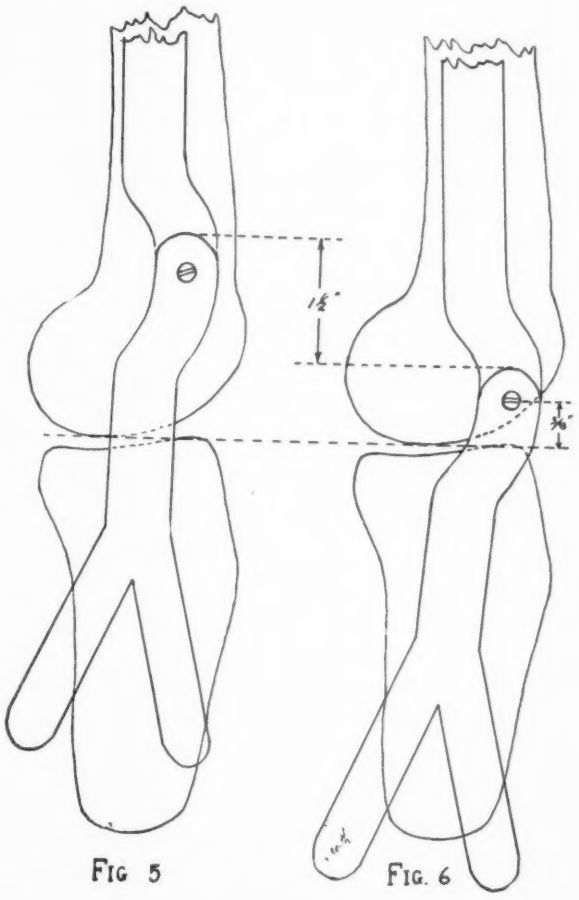

FIG 5 FIG. 6

Figure 7 shows the flexed position. Note that the long axis of the prosthesis A–B and that of the stump C–D are parallel. This insures a parallel relationship between the anterior tibial crest and the front of the prosthesis. Thus, when the leg is extended there will be an equal distribution of pressure along a broad area of the tibial crest. See bracket E as compared with the small pressure point E in Figure 1. Now compare Figure 4 and Figure 7 and note that in the latter the prosthesis is held well up on the stump in spite of having to lengthen the lower brace. This is accomplished by the anterior offset of the joint axis.

SUMMARY.—1. A case has been presented of a patient with a below-knee amputation who complained of painful pressure on the anterior tip of the stump where it contacted his prosthesis while manipulating the prosthesis in a position of flexion.

2. An attempt has been made to illustrate and explain how, in this particular case, the pain was caused.

3. A solution to the problem has been presented and illustrated.

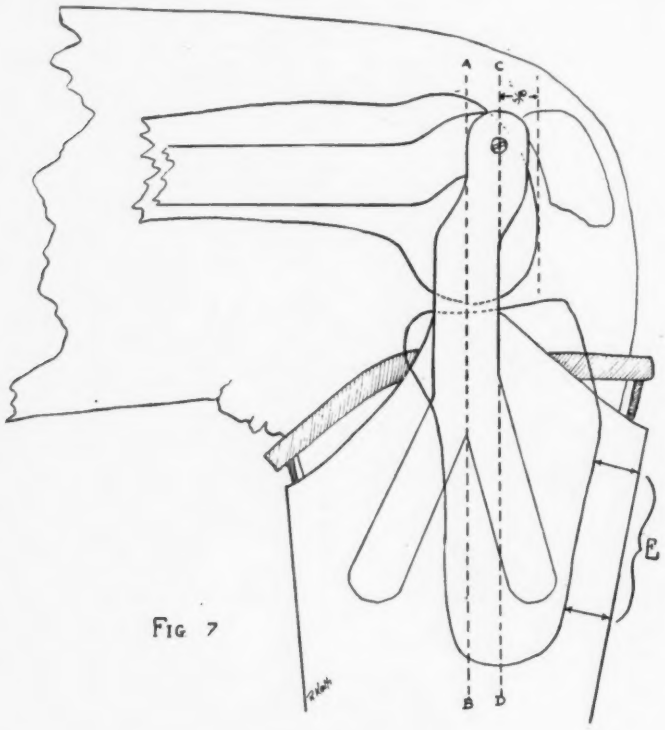

FIG 7

CONCLUSION

This is a single case, and further study will be necessary to prove the value of the suggested change in the type of prosthetic joint. The change, however, is based on fundamental principles of mechanics and, therefore, should hold true for all below-knee amputations. In the near future, there will undoubtedly be many below-knee amputations requiring prostheses, and it is also reasonable to presume there will be many complaints registered similar to those of the patient mentioned in this paper. The proposed joint is of a more simple construction; it should be less expensive to manufacture and require less frequent repair subsequent to the original fitting.

THE RACIAL DISTRIBUTION OF CANCER

II—TUMORS OF THE KIDNEY, BLADDER AND MALE GENITAL ORGANS*

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IN A PREVIOUS COMMUNICATION[7] methods were presented for the analysis of the racial distribution of cancer. The percentage colored (*i.e.*, the ratio of colored patients to all patients) was determined for each tumor studied, and was compared to the percentage colored for a control group. This group consisted of all patients with cancer except those with certain types of tumors. The work is continued in this study on the racial distribution of tumors of the kidney and bladder in both sexes and of the male genital organs.

Carcinoma of the Kidney.—According to the data of Hines Hospital (Table I), the percentage colored for carcinoma of the kidney (5.64 per cent of 195 patients) did not deviate appreciably from that of the control group (8.45 per cent of 8,572 men). An analysis of only those cases, which were diagnosed histologically, as transitional carcinoma of the renal pelvis showed approximately the same percentage colored as the control. Similarly, an analysis of the data of the U. S. Public Health Service[1, 2, 3, 4, 6, 8, 9] showed no significant differences in the racial distribution for tumors of the kidney and for the control group (6.49 and 5.61 per cent colored, respectively, for men and 4.76 and 6.83 for women [Table I]). In none of the localities surveyed was there any significant difference between the percentage colored for renal cancer and for the corresponding control. The mortality statistics[5] also showed approximately the same percentage colored for tumors of the kidney (4.57 for men and 4.40 per cent for women) and for the control groups (4.75 and 5.27).

According to the data from the three sources, the racial distribution of cancer of the kidney is the same as that for the control groups.

Tumors of the Bladder.—Of 430 men with carcinoma of the bladder in Hines Hospital, only 4.88 per cent were colored. This is significantly lower than the 8.45 per cent for the control. Low percentages were also observed for papilloma of the bladder (2.36 per cent of 127 patients).

In surveys of five geographic areas, the U. S. Public Health Service reported 654 male patients with tumor of the bladder. Only 1.98 per cent of the patients were colored. This is significantly lower than the 5.61 per cent colored for the control. In each of the five localities, the percentage

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colored for tumors of the bladder was lower than the corresponding control. According to the mortality statistics, the percentage colored for tumors of the bladder in men (3.72 per cent) is also significantly lower than the control percentage (4.75 per cent).

It seems then that in men tumors of the bladder occur in relatively few colored individuals. In women no significant differences were observed in

TABLE I

THE RACIAL DISTRIBUTION OF TUMORS OF THE GENITO-URINARY TRACT ACCORDING TO DATA FROM HINES HOSPITAL, THE SURVEY OF THE U. S. PUBLIC HEALTH SERVICE, AND THE U. S. MORTALITY STATISTICS

	Percentage Colored					Number of Individuals, All Cases				
	Male			Female		Male			Female	
	Hines Hosp.	Public Health Survey	Mortality Statistics	Public Health Survey	Mortality Statistics	Hines Hosp.	Public Health Survey	Mortality Statistics	Public Health Survey	Mortality Statistics
Cancer, all types	6.29	4.24	4.61	8.32	7.00	11,790	19,615	278,860	24,735	336,844
Benign lesions, all types	5.82	—	—	—	—	1,699	—	—	—	—
Control groups:										
Cancer	8.45†	5.61‡	4.75‡	6.83§	5.27§	8,572	14,022	265,993	15,100	256,945
Benign lesions	8.50¶	—	—	—	—	1,106	—	—	—	—
Kidney: Cancer	—	6.49	4.57	4.76	4.40	—	231	4,983	126	3,816
Kidney: Carcinoma	5.64	—	—	—	—	195	—	—	—	—
Bladder: Cancer	—	1.98*	3.72*	5.74	5.70	—	654	13,145	261	5,985
Bladder: Carcinoma	4.88*	—	—	—	—	430	—	—	—	—
Bladder: Papilloma	2.36*	—	—	—	—	127	—	—	—	—
Prostate: Cancer	—	7.58*	4.84	—	—	—	1,490	27,447	—	—
Prostate: Carcinoma	11.23*	—	—	—	—	374	—	—	—	—
Penis: Carcinoma	27.50*	—	—	—	—	120	—	—	—	—
Other genito-urinary sites: Cancer	—	—	14.74*	—	—	—	—	1,411	—	—
Scrotum: Cancer	—	—	13.71*	—	—	—	—	151	—	—
Scrotum: Carcinoma	25.	—	—	—	—	8	—	—	—	—
Testis: Cancer	—	—	2.60*	—	—	—	—	1,803	—	—
Testis: Carcinoma	3.04*	—	—	—	—	263	—	—	—	—

* The percentage colored is significantly different from that of the corresponding control group.

Composition of Control Groups:

† All male patients with cancer except those with carcinoma of the exposed skin and lip.
‡ All men with cancer except those with cancer of the skin and lip.
§ All women with cancer except those with cancer of the skin, lip, uterus and cervix.
¶ All male patients with benign lesions except those with keratosis and leukoplakia.

the percentage colored for cancer of the bladder and of the control groups (5.74 and 6.83 per cent, respectively, for the U. S. Public Health Survey and 5.70 and 5.27 per cent for the mortality statistics).

Carcinoma of the Prostate.—Hines Hospital had 374 men with carcinoma of the prostate, and 11.23 per cent of the patients were colored. This percentage is significantly higher than that of the control group (8.45 per cent).

An analysis of the data of the U. S. Public Health Service gave 7.58 per cent colored of 1490 men with tumors of the prostate. Although this percentage is greater than the 5.61 per cent colored for the control, the difference is not statistically significant (P—0.07). The mortality statistics for tumors of the prostate gave approximately the same percentage colored (4.84 per cent) as the control (4.75 per cent).

The results obtained from the three sources are, for this tumor, not

consistent, and no definite conclusions can be drawn. It is probable that a slightly larger number of colored men develop cancer of the prostate than white men.

Cancer of the Penis.—Carcinoma of the penis was diagnosed in 120 patients in Hines Hospital. This group of men had the extraordinarily high figure of 27.5 per cent colored, which is considerably and significantly higher than the 8.45 per cent for the control group.

In the mortality statistics, cancer of the penis is included in the category "Other Male Genito-urinary Tumors." The percentage colored for this group of tumors is 14.74 per cent, which is much higher than the control 4.79 per cent.

It is quite definite that an extraordinarily large percentage of patients with tumors of the penis is colored.

Cancer of the Scrotum.—Scrotal tumors are rare, and only eight cases were observed in the hospital. Of these, two were colored. The mortality statistics record 151 deaths with this tumor, and 13.71 per cent were colored. This percentage is approximately the same as that for tumors of the penis (14.74 per cent), and is significantly higher than the control.

Patients with tumors of the scrotum, then, like those with cancer of the penis, occurred in a relatively large number of colored men.

Cancer of the Testis.—Hines Hospital had 263 patients with tumor of the testis and, of these, only 3.04 per cent were colored. This percentage is significantly lower than that for the control group.

The mortality statistics gave a percentage colored of 2.60 per cent as compared to a control of 4.75 per cent. Further analysis of the data showed that in the older age-groups (50 years or over) the percentage colored for tumors of the testis is approximately the same as the corresponding control. It seems that young patients with tumor of the testis have a relatively low percentage colored, whereas older men with this tumor have the same percentage colored as the control group. The findings suggest that testicular cancer occurred less frequently in young Negroes than in young white men, but in older individuals the tumor was equally common in the two races.

Discussion.—Surprisingly good agreement on the racial distribution of patients with genito-urinary tumors was obtained by analyses of the statistics from three diverse sources, namely, (1) patients of Edward Hines Jr. Memorial Hospital; (2) the survey on cancer by the Public Health Service; and (3) the mortality statistics of the United States. This agreement suggests that the observations are significant both statistically and biologically.

It was noted that patients with tumors of the penis and scrotum had a relatively high percentage colored and those with cancer of the prostate had possibly a slightly higher percentage colored than the control groups. On the other hand, men with neoplasms of the bladder and testis had low percentages colored. Cancer of the kidney in men and women and cancer of the bladder in women had approximately the same racial distribution as the control groups.

The observed high percentage colored in patients with cancer of the penis and scrotum may be attributed to extrinsic environmental factors, such as local unhygienic conditions and chronic inflammatory processes. The biologic factors responsible for the low percentage colored for cancer of the bladder and testis are not evident. It is even hazardous to guess whether extrinsic environmental factors or intrinsic racial differences in susceptibility are involved.

SUMMARY

The incidence of cancer of the genito-urinary tract in the white and colored race was studied indirectly by the method of determining the percentage colored for the tumor and for a control group.

According to this method, cancer of the penis and scrotum and possibly cancer of the prostate occurred relatively more frequently in colored than in white men. Colored men below age 50 had a relatively low incidence of cancer of the testis, but Negroes above age 50 had the same incidence of this tumor as white men. Colored men but not colored women had a relatively low incidence of cancer of the bladder. Tumors of the kidney occurred equally frequently in white and colored individuals.

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BRIEF COMMUNICATION

AN UNUSUAL CASE OF PENETRATING FOREIGN BODY IN THE MEDIASTINUM

CASE REPORT

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THE FOLLOWING CASE is presented because of its unusual nature with respect to the type of foreign body; the mode of introduction into the mediastinum; the absence of serious injury to vital structures; and the interesting surgical problem presented in its removal.

Case Report.—New Haven Hospital No. B-48156: M. V., white, female, age 57, was admitted to the Surgical Service October 21, 1943. For several weeks she had been in a psychiatric hospital, with a diagnosis of manic-depressive psychosis. On the day of admission, she managed to secrete a straight steel crochet hook on her person. About two hours before admission, with suicidal intent, she forced the crochet hook through the skin of the jugular notch until it was lost in the depth of the tissues. After a brief period of remorse, she informed a nurse of her action. In view of the patient's good physical condition and the absence of any significant external wound, the nurse was inclined to discredit the patient's story, but wisely called the physician in charge who ordered roentgenograms of the chest (Figs. 1 and 2). This revealed the crochet hook lying in the mediastinum and bent at an angle of 45 degrees. The patient was immediately transferred to the Thoracic Service.

Physical Examination.—The patient appeared as an hyperkinetic, slightly disoriented, elderly white female in apparently good physical condition. She complained only of slight pain in the posterior thoracic midline and reiterated her desire to die. Pulse 72, the rhythm regular; blood pressure 172/94. There was a pinpoint, dry wound in the jugular notch; no foreign body could be felt under it. There was no evidence of cyanosis, no subcutaneous emphysema of neck or chest, no dyspnea, and only moderate hyperpnea (respirations 38). The lung fields were clear to percussion and auscultation; there was no pleural or pericardial friction rub. The abdomen was negative to palpation. The pulses of the lower extremities were full and equal; the femoral blood pressures were equal bilaterally.

Operation.—Approximately one hour after admission, anesthesia was induced with nitrous oxide and cyclopropane; the trachea was intubated, and insufflation of ether-oxygen mixtures begun. With the patient in the supine position, the entire anterior and lateral chest including the lower neck was prepared and draped. A submammary incision was made on the left and, after elevating a flap of breast and pectoral muscles, the anterior half of the fourth rib and cartilage was resected. On opening the left pleural cavity, there was no evidence of preëxisting pneumothorax or bloody effusion; the mediastinal pleura appeared quite normal; there was no emphysema. The mediastinal pleura was opened just behind the phrenic nerve above the pulmonary hilus, uncovering the pulmonary artery, which was uninjured. The foreign body could not be felt. The lung was then retracted forward and the posterior mediastinal pleura incised. Behind the proximal portion of the left primary bronchus the end of the

hook was quickly exposed. It was cut off with a heavy shears. The shaft of the hook was then easily manipulated into the pleural cavity and removed (Fig. 3). The mediastinal pleural defect was allowed to remain open for drainage and the chest closed in layers, with silk, reëxpanding the lung with slight positive pressure and by aspiration of the residual pneumothorax. About 5 Gm. of sulfathiazole powder was dusted into the mediastinal area and pleural cavity during closure. Operation time 90 minutes.

Convalescence was uneventful. The patient received sulfadiazine therapy for eight days, at which time she was afebrile and ambulatory. The wound healed *per primam;* the left lung expanded well without significant pleural effusion, and she was discharged to the Psychiatric Service on the ninth postoperative day.

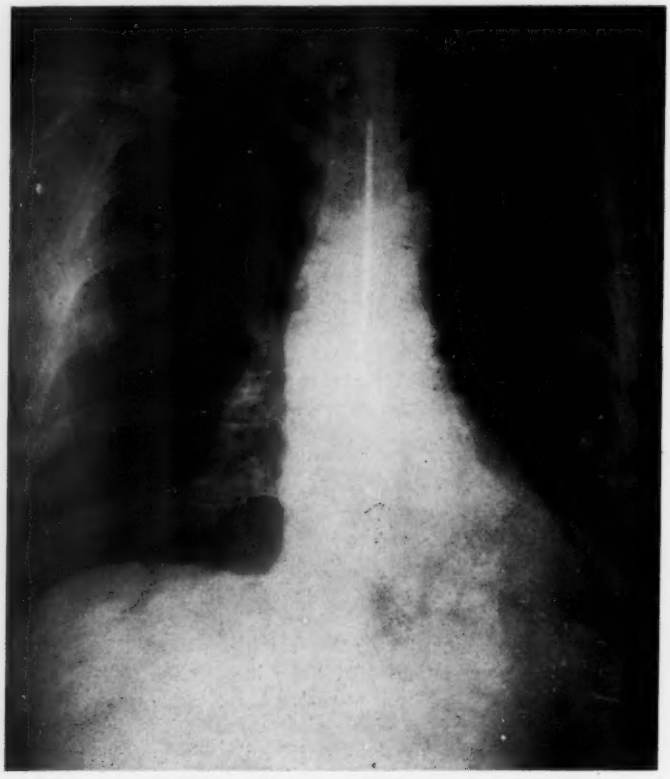

FIG. 1.—Preoperative postero-anterior roentgenogram of chest.

DISCUSSION.—The possible treatment of this patient's surgical problem presented several alternatives:

1. Conservative or nonoperative management with chemotherapy in an attempt to control possible mediastinitis. In favor of this course was the mental status of the patient. Against it was the high probability of secondary pressure erosion of a large vessel or the esophagus.

2. Surgical removal of the hook, by retrograde extraction in the jugular notch under local anesthesia. In favor of this procedure was its apparent

simplicity and the avoidance of major thoracotomy. Against this procedure were the fact that the needle could not be palpated in the neck, its evident angulation, and the presence of a hooked end which could easily produce a tear of vital structures during withdrawal. Furthermore, this route would not give the opportunity to examine directly for complications in the mediastinum and to attempt their control, if found to be present.

FIG. 2.—Preoperative lateral roentgenogram of chest.

3. Transthoracic mediastinotomy: This was the procedure of choice, in view of the considerations mentioned above.

It is interesting to speculate on the probable course of this foreign body as it entered the superior mediastinum, in order to explain its final location and its failure to penetrate the trachea, esophagus or large vessels. Having been introduced by a right-handed person, it doubtlessly inclined slightly downward and to the left, slipped above the left innominate vein, grazed the

trachea, slid over the arch of the aorta between the innominate artery and the left internal carotid, and missed the left border of the esophagus. Impinging on a vertebral body, a second hard push (as described by the patient) angulated it. Its point then passed inferiorly to rest behind the left pulmonary artery and left primary bronchus, in which position it was discovered at operation.

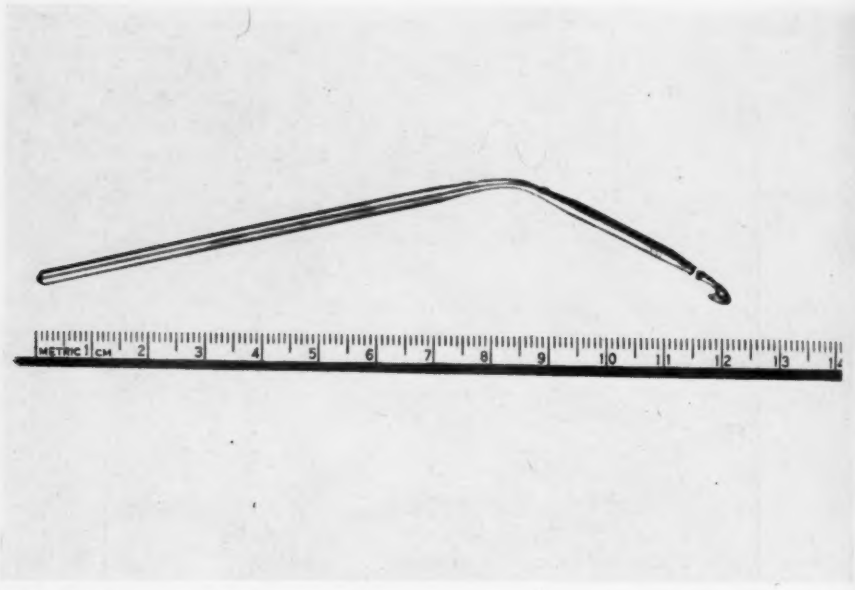

FIG. 3.—Photograph of the foreign body, showing point of section and angulation of the shaft.

SUMMARY

An unusual case of penetrating mediastinal foreign body (steel crochet hook) is presented. The considerations determining the method of removal and the probable anatomic course of the penetration are discussed.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

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Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.